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Expert Report of Professor Meredith Rosenthal

March 25, 2019

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I. QUALIFICATIONS

1. My name is Meredith B. Rosenthal. I am the C. Boyden Gray Professor of Health Economics and Policy at the Harvard T.H. Chan School of Public Health and an Academic Affiliate of Greylock McKinnon Associates (“GMA”), a consulting and litigation support firm. My principal research interests concern the economics of the health care industry.

2. At Harvard, I have taught in undergraduate, Masters- and Ph.D.-level health economics and health policy courses. Since 1996, I have worked on a number of consulting matters through GMA, most of which relate to litigation in health care markets generally and the pharmaceutical industry in particular. I have also submitted written testimony in litigation concerning alleged anticompetitive conduct for a variety of drugs, which are listed in Attachment A. Most relevant to the current matter, I have submitted written and in some cases presented oral testimony in litigation concerning allegations of improper marketing of the following prescription drugs: Actiq,¹ Bextra,² Celexa and Lexapro,³ Lyrica and Zyvox,⁴ Geodon,⁵

¹ *In re: Actiq Sales and Marketing*, United States District Court for the Eastern District of Pennsylvania, No. 07-CV-4492.

² *In re: Bextra Marketing Sales Practices and Product Liability Litigation*, United States District Court for the Northern District of California, MDL No. 1699, No. M:05-CV-01699-CRB.

³ *In re: Celexa and Lexapro and Sales Practices Litigation*, United States District Court for the District of Massachusetts, Case No. 09-MD-2067 (NMG); MDL No. 2067.

⁴ *Mary K. Jones v. Pfizer Inc., et al.*, United States District Court for the Southern District of New York, Civil Action No. 1:10-cv-03864-AKH.

⁵ *In re United States of America v. Pfizer, Inc.*, United States District Court for the District of Massachusetts, Case No. 1:10-CV-11166-DPW.

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Ketek,⁶ Lupron,⁷ Neurontin,⁸ Nexium,⁹ Premarin, Prempro and Premphase,¹⁰ Risperdal,¹¹
 Rituxan,¹² Vioxx¹³ and Zyprexa.¹⁴

3. I have conducted research on a wide variety of health economics topics, with a focus on the financing and organization of the U.S. health care system. Specific topics I have studied include the effect of payment incentives on provider behavior,¹⁵ payment and delivery system

⁶ *Sergeants Benevolent Association Health and Welfare Fund v. Sanofi-Aventis U.S. LLP*, United States District Court for the Eastern District of New York, No. 08-CV-179.

⁷ *In re: Lupron Marketing and Sales Practices Litigation*, United States District Court for the District of Massachusetts, MDL No. 1430, No. 01-CV-10861.

⁸ *In re: Neurontin Marketing and Sales Practices Litigation*, United States District Court for the District of Massachusetts, MDL No. 1629, No. 04-10981; *Gregory Clark and Linda Meashey v. Pfizer Inc., and Warner-Lambert Company, LLC*, Philadelphia County Court of Common Pleas, No. 1819; *Elizabeth Judy and Stephen Brown v. Pfizer, Inc.*, individually and as successor in interest to Parke-Davis and Warner-Lambert, Inc., Circuit Court of the City of St. Louis, State of Missouri, Cause No. 042-01946, Division No. 1; and *In re: Neurontin Marketing and Sales Practices Litigation*, as it relates to: *Kaiser Foundation Health Plan v. Pfizer, Inc.*, United States District Court for the District of Massachusetts, MDL No. 1629, No. 04-10981-PBS, No. 04-10739-PBS.

⁹ *Commonwealth Care Alliance and Glen Crenshaw v. AstraZeneca Pharmaceuticals L.P. and Zeneca Holdings, Inc.*, Commonwealth of Massachusetts, Superior Court, Trial Court Department, No. 05-CV-0269 BLS.

¹⁰ *Krueger v. Wyeth, Inc.*, United States District Court for the Southern District of California, Civil Action No. 03CV2496 JAH (AJB).

¹¹ *Charles Foti, Attorney General ex rel. State of Louisiana v. Janssen Pharmaceutica, Inc.*, 27th Judicial District Court, Parish of St. Landry, No. 04-C-3967-D and *The State of Texas, ex rel. Allen Jones v. Janssen, L.P.*, District Court, 250th Judicial District, Travis County, Texas, No. D-1GV-04-001288.

¹² *United States ex rel. John Underwood v. Genentech, Inc.*, United States District Court for the Eastern District of Pennsylvania, No. 03-CV-3983.

¹³ *Kleinman v. Merck & Co.*, No. ATL-L-3954-04 and *Martin v. Merck & Co.*, No. ATL-L24-05, Superior Court of New Jersey, Law Division, Camden County.

¹⁴ *In re: Zyprexa Products Liability Litigation*, United States District Court for the Eastern District of New York, MDL No. 1596, Civil Action No. 05-CV-4115. I also submitted testimony in related state matters.

¹⁵ See M. Rosenthal, "Risk Sharing and the Supply of Mental Health Services," *Journal of Health Economics*, 19(6), November 2000, pp. 1047-65; M. Rosenthal, R. Frank, Z. Li, and A. Epstein, "From Concept to Practice: Early Experience with Pay-for-Performance," *Journal of the American Medical Association*, 294(14), October 2005, pp. 1788-93; and M. Rosenthal, Z. Li, A. Robertson, and A. Milstein, "Impact of Financial Incentives for Prenatal Care on Birth Outcomes and Spending," *Health Services Research*, 44(5), Part 1, October 2009, pp. 1465-79.

reform,¹⁶ and advertising and promotion of prescription drugs.¹⁷ I have published more than 150 peer-reviewed journal articles, essays, and book chapters.

4. I received an A.B. in International Relations from Brown University in 1990 and a Ph.D. in Health Policy (Economics Track) from Harvard University in 1998. A more complete description of my qualifications is found in my *Curriculum Vitae*, which is included as Attachment A to this Report.

5. I am being compensated at a rate of \$825 per hour for my time. The compensation due to me is for the work performed and it is not contingent upon my opinions, my conclusions, or the outcome of this matter. The opinions I state in this report are stated within a reasonable degree of professional certainty in the areas of healthcare economics and econometrics. I reserve the right to respond to, rebut, opine on, or incorporate opinions offered by other experts in these matters.

¹⁶ See M. Rosenthal, "Beyond Pay for Performance: Emerging Models of Provider-Payment Reform," *The New England Journal of Medicine*, 359(12), September 2008, pp. 1197-1200; M. Rosenthal, M. Friedberg, S. Singer, D. Eastman, Z. Li, and E. Schneider, "Effect of a Multipayer Patient-Centered Medical Home on Health Care Utilization and Quality: The Rhode Island Chronic Care Sustainability Initiative Pilot Program," *JAMA Internal Medicine*, September 2013, PMID: 24018613; and S. Edwards, M. Abrams, M. Rosenthal, *et al.*, "Structuring Payment to Medical Homes After the Affordable Care Act," *Journal of General Internal Medicine*, 2014, PMID: 417661.

¹⁷ M. Rosenthal, *et al.*, "Promotion of Prescription Drugs to Consumers," *The New England Journal of Medicine*, 346(7), February 2002, pp. 498-505; M. Rosenthal, *et al.*, "Demand Effects of Recent Changes in Prescription Drug Promotion," *Forum for Health Economics & Policy*, 6(1), January 2003, pp. 1-26; M. Mello, M. Rosenthal, and P. Neumann, "Direct-to-Consumer Advertising and Shared Liability for Pharmaceutical Manufacturers," *Journal of the American Medical Association*, 289(4), January 2003, pp. 477-81; J. Donohue, E. Berndt, M. Rosenthal, A. Epstein, and R. Frank, "Effects of Pharmaceutical Promotion on Adherence to the Treatment Guidelines for Depression," *Medical Care*, 42(12), December 2004, pp. 1176-85.

II. ASSIGNMENT

6. I understand that this litigation, brought by the City of Cleveland, the City of Akron, Cuyahoga County and Summit County (collectively the “Bellwether governments”), alleges among other things that the “Defendants’ conduct in promoting opioid use, addiction, abuse, overdose and death has had severe and far-reaching public health, social services, and criminal justice consequences, including the fueling of addiction and overdose from illicit drugs such as heroin.”¹⁸ The governments further allege that the opioid epidemic and the need for increased services “arose from the opioid manufacturers’ deliberately deceptive marketing strategy to expand opioid use, together with the distributors’ equally deliberate efforts to evade restriction on opioid distribution.”¹⁹

7. In this Report, I refer to the manufacturers’ deceptive marketing strategy and tactics as “manufacturer misconduct.” This report does not address non-marketing misconduct.

8. My assignment is to answer the following questions framed by plaintiffs’ counsel, all to a reasonable degree of certainty in the area of healthcare economics and econometrics:

- *Manufacturer substantial contribution causation.* Do you have an opinion as to whether the combined effect of the Defendant manufacturers’ promotion of prescription opioids

¹⁸ Second Amended Complaint, *In Re National Prescription Opiate Litigation*, MDL No. 2804, Case No. 17-md-2804, United States District Court for the Northern District of Ohio, Eastern Division, May 18, 2018 (hereafter Cuyahoga Complaint), ¶ 19; and Corrected Second Amended Complaint, *In Re National Prescription Opiate Litigation*, MDL No. 2804, Case No. 17-md-2804 (referring to Case No. 18-op-45090), United States District Court for the Northern District of Ohio Eastern Division, May 18, 2018 (hereafter Summit Complaint), ¶ 20. I refer to both complaints as the Complaints.

¹⁹ Cuyahoga Complaint, ¶ 3 and Summit Complaint, ¶ 3.

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since 1995 was a substantial contributing factor in causing an increase in the use of prescription opioids in the Bellwether communities?

- *Manufacturer “but for” causation.* Do you have an opinion as to whether the increase in the use of prescription opioids in the Bellwether communities since 1995 would have occurred were it not for, i.e., “but for,” the allegedly unlawful promotion of these products by the Defendant manufacturers?
- *Extent of “but for” causation.* Do you have an opinion as to the quantum of increase in the use of prescription opioids in the Bellwether communities that resulted from the Defendant manufacturers’ promotion of prescription opioids since 1995?
- *Sensitivity to particular manufacturers.* To what extent are your opinions sensitive to the potential that the fact finder concludes that any one or more of the Defendant manufacturers is found not to have engaged in unlawful marketing? If so, please explain and, if necessary, articulate the sensitivity in quantitative terms such that your conclusions may be used by other experts in reports that use your results to estimate damages.

III. LIST OF MATERIALS CONSIDERED

9. The materials I considered are listed in Attachment B. The staff that worked under my direction had full and complete access to the documents and data produced in this case.

IV. OVERVIEW OF STRUCTURE AND ORGANIZATION OF CHAPTER

10. In the remainder of this chapter, I review the economic basis for my opinions that the allegedly unlawful practices caused an increase in sales of prescription opioids. In Section VI, I discuss the relevant features of the prescription drug market that form the institutional context within which the alleged violations took place. In that section, I also describe how pharmaceutical companies, including the Defendants in this matter, influence the key decision makers in pharmaceutical markets (payers, physicians and patients) through the use and alleged misuse of information and marketing tactics. I also review the substantial scientific literature on the impact of commercial sources of information on physician prescribing behavior. This literature shows that physicians are influenced by commercial promotional messages, even if when asked they do not acknowledge those influences. In Section VII, I present evidence specific to the marketing of opioids, including scientific literature and the Defendants' own documents showing that they recognized the importance of promotion in increasing sales of their opioid products. In Section VIII, I provide a detailed description of my econometric methodology to quantify directly the causal relationship between promotion and sales (I refer to this later as "the direct approach") and I present the results of this analysis. In Section IX, I propose and implement an indirect model of changes in demographic, economic and medical conditions as an additional approach that explains the growth in opioid sales from marketing and which avoids some measurement challenges inherent in the first approach. In Section X, I present a final set of analyses to test the fairness and reasonableness of the results from my direct and indirect methodologies. In particular, I discuss the hypothetical impact of

changes in pain management over time as an alternative theory explaining the growth in opioid sales. My conclusions appear in Section XI.

V. SUMMARY OF OPINIONS

11. Based on my expertise in healthcare economics and econometrics, as well as research and data analysis specific to this matter, I reach the following conclusions, all to a reasonable degree of certainty in the areas of healthcare economics and econometrics:

- Promotion of pharmaceuticals increases their sales. Such promotion is particularly important for goods like pharmaceuticals, which require trial for consumers to ascertain their worth. Promotion is also very profitable in this industry due to factors such as third-party coverage, which cause prices to exceed production costs by a large margin.
- The alleged unlawful promotion of opioids, if proven, resulted in increased sales of opioids. Economic theory and empirical studies in the economics, marketing, and health services research literature find that promotional efforts increase both approved and unapproved uses of pharmaceuticals. The Defendants' strategic marketing materials corroborate this conclusion. As a result, I am of the opinion that the combined effect of the Defendant manufacturers' promotion of prescription opioids since 1995 was a substantial contributing factor to the increase in the use of prescription opioids in the Bellwether communities.
- Using econometric models, I demonstrate that I can reasonably identify the extent to which the sale of prescription opioids (measured by the number of milligrams of morphine equivalents, or MMEs) was caused by any quantum of the Defendants'

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promotional efforts that counsel can prove was unlawful. Based upon my analyses and assumptions from counsel about the extent of promotion that can be proven to be unlawful, I can reasonably identify approximately 45-67% of MMEs during the period of my analysis as caused by unlawful promotion. I report my estimates in further detail below, by year both nationally and for the Bellwether counties.

- As per my assignment, should the conduct of any manufacturer Defendant be excluded from consideration at the trial of this litigation for any reason, I am able to calculate the number of additional prescriptions caused by the allegedly unlawful promotion of any combination of remaining Defendants.

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Summary of Opinions		
Section	What I Did	What I Found
VI	Reviewed the economic and institutional landscape surrounding the market for pharmaceuticals, including the role of physician agency, insurance, and the role of promotion. I also summarize what is known about marketing tactics impact.	<ul style="list-style-type: none"> ○ Promotion of pharmaceuticals increases sales. ○ Promotion is important for pharmaceuticals because they are experience goods. Patients and doctors are relatively insensitive to price, which increases prices and spending making promotion more profitable than for typical commodities.
VII	Reviewed literature on marketing of opioids and show examples from discovery that corroborate the economic theory and evidence on pharmaceutical marketing.	<ul style="list-style-type: none"> ○ Literature demonstrates widespread transfers of value (payments and in-kind transfers) to physicians by opioid manufacturers. ○ Discovery materials show examples of diverse marketing tactics, recognition of promotional effectiveness.
VIII	Proposed and implemented a direct method of estimating the impact of Defendant promotion on sales (MMEs)	<ul style="list-style-type: none"> ○ Peer-reviewed literature provides examples of accepted econometric methods to measure the impact of promotion on sales using aggregate time-series data. ○ Application of this direct method of estimation shows that Defendants' promotion was a substantial contributing factor to the growth in sales of opioids. ○ The challenged promotion led to excess MMEs of 45% between 1995 and 2018.
IX	Propose and implement an indirect method of estimating the effect of Defendant promotion on sales	<ul style="list-style-type: none"> ○ Peer-reviewed literature provides examples of indirect (residual) methods to measure the impact of promotion on sales using aggregate cross-sectional data. ○ Application of this indirect method of estimation shows that Defendants' promotion led to excess MMEs of 67% between 1995 and 2016.
X	Examined whether the growth of opioids could be explained by appropriate use using a hypothetical where all patients who clearly benefit from opioids received guideline-based treatment	<ul style="list-style-type: none"> ○ Hypothetical treatment of 100% of key patient groups (end-of-life cancer, trauma, and surgical) with guideline-based dosages and durations would consume only a small fraction (10.7%) of actual MMEs between 1995 and 2018.

VI. INDUSTRY BACKGROUND

A. Pharmaceutical Demand

12. To understand the rationale for and impact of the Defendant manufacturers' alleged behavior, it is necessary to consider both the institutional context of the pharmaceutical industry and health care financing. Pharmaceutical markets have features that increase the incentives to engage in deceptive marketing schemes; deceptive marketing is both harder to detect and more profitable than in many other markets. In this section, I describe the relevant features of the prescription drug market, regulatory issues, and third-party reimbursement for prescription drugs.

13. By way of preface to this section, I highlight several overarching points that are essential to the application of economics to the matter at hand. Economic analysis of pharmaceutical markets must take into account three key features: (1) the role of physicians as designated decision makers (in economic terms, "agents") for both individual patients and payers; (2) information problems that patients, physicians and payers face in evaluating the value of a given drug; and (3) the role of public and private third-party payers (*e.g.*, health insurance).

Physician Agency

14. Prescription drugs, unlike typical commodities, can only be purchased with a physician's authorization. Thus, physicians act as a trusted intermediary in prescription drug decision making. While patient preferences play a role in the choice of therapy, physicians have enormous influence over health care decisions, particularly for serious medical conditions.²⁰

²⁰ See, for example, J. Donohue, M. Cevalco and M. Rosenthal, "A Decade of Direct-to-Consumer Advertising of Prescription Drugs," *New England Journal of Medicine*, 357(7), 2007, pp. 673-81. Also see Congressional Budget

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Professional norms encourage physicians to use their clinical skills, knowledge and experience to make therapeutic choices that are in the best interest of their patients. In practice, however, physicians face numerous constraints, including limited time and ability to digest the continuous flow of information about new treatments.²¹ In many situations, then, physician prescription decisions can be heavily influenced by accessible but sometimes imperfect information, e.g., detailing visits; published guidelines, algorithms or other practice standards; journal advertising. These limitations extend to decision-making about off-label uses of prescription drugs as well. Survey data suggest a very mixed picture of physician knowledge about the FDA-approved uses – as well as unsafe ones (e.g., uses for which a black-box warning has been issued) – of common products.²²

Office (CBO), “Promotional Spending for Prescription Drugs,” December 2, 2009; Families USA, “Off the Charts: Pay, Profits and Spending by Drug Companies,” Families USA Publication No. 01-104, July 2001, pp. 1-31 at 1; M. Hurwitz and R. Caves, “Persuasion or Information? Promotion and the Shares of Brand Name and Generic Pharmaceuticals,” *Journal of Law and Economics*, 31(2), 1988, pp. 299-320 at 302.

²¹ F. Scherer, “The Pharmaceutical Industry” in *Handbook of Health Economics*, eds. A. Culyer and J. Newhouse, Amsterdam: Elsevier/North-Holland, 2000, pp. 1297-1336 at 1300-02.

²² D. Chen, *et al.*, “U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: Results of a national survey,” *Pharmacoepidemiology and Drug Safety*, 18(11), 2009, 1094-1100.

Imperfect Information About Pharmaceutical Products

15. Both physicians and patients face an information problem in selecting pharmaceutical treatments that challenges typical conclusions about well-functioning markets.²³ Prescription drugs fit the economic definition of “experience goods” – they need to be tried for a patient to know their value.²⁴ A product that is safe and effective on average may cause side effects in some patients and have differential effectiveness based on both known and unknown factors. Because some risks and benefits may be observed only over the long term and may be hard to attribute clearly to a drug, even experience may not lead patients and their physicians to fully understand the risks and benefits of a product. For example, if a patient on a cholesterol medication does not have a stroke, is that because of the medication or other protective factors such as non-smoking status? Likewise, some risks may occur long after the initial prescription and may not be brought to the prescribing physician’s attention, preventing learning and adaptation from occurring. For example and in the present matter, the stigma associated with opioid addiction likely compounded the information problems faced by physicians – patients might have tried to mask their addiction, rather than making their physicians aware of these negative “side effects”.²⁵ In light of these information problems, it

²³ Economics Nobel Laureate, Kenneth Arrow has recognized this in his published research. K. Arrow, “Uncertainty and the Welfare Economics of Medical Care,” *The American Economic Review*, 53(5), 1963, pp. 941-73.

²⁴ For experience goods, see P. Nelson, “Information and consumer behavior,” *Journal of Political Economy* 78(2), 1970, pp. 311-29. See also M.R. Darby and E. Karni, “Free competition and the optimal amount of fraud,” *Journal of Law and Economics*, 16(1), 1973, pp. 67-88. In some cases, prescription drugs have been labeled credence or experience goods because their full effects are not easily observed even after some time. For example, see E.R. Berndt, “Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price,” *Journal of Economic Perspectives*, 16(4), 2002, pp. 45-66. See also T. Iizuka, “Experts’ Agency Problems: Evidence from the Prescription Drug Market in Japan,” *Rand Journal of Economics*, 38(3), 2007, pp. 844-62.

²⁵ M. Botticelli and H. Koh, “Changing the Language of Addiction,” *Journal of the American Medical Association*, 316(13), 2016, pp. 1361-62.

would be reasonable to expect that market forces alone would fail to protect consumers against false claims of product efficacy and safety.

The Role of Public and Private Health Insurance

16. Another distinguishing feature of pharmaceutical demand is the widespread presence of insurance coverage. As of 2017, approximately 88% of non-elderly adults have insurance coverage through a private or public health insurance plan. Since the passage of the Affordable Care Act in 2010, prescription drug coverage has been required as part of the essential health benefits offered by “qualified health plans” (those that meet the legislation’s individual and employer mandates). Insurance coverage among the elderly is virtually universal and among those enrolled in Medicare the vast majority have prescription drug coverage either through Medicare Part D or a retiree plan.²⁶ Moreover, insurance coverage is relatively comprehensive: between 2003 and 2017 the out-of-pocket share of total prescription drug spending dropped from 26% to 14%.²⁷ The small share of prescription drug spending that is paid for out-of-pocket by U.S. consumers reflects the prevalence of fixed dollar copayments as the most common form of cost sharing. Even when copayments are tiered, the top copayment often reflects a small share of the full retail price of a drug. The implication of generous insurance coverage is

²⁶ Kaiser Family Foundation, “Medicare Prescription Drug Plans: Distribution of Medicare Beneficiaries with Creditable Prescription Drug Coverage, by Type” (<http://kff.org/medicare/state-indicator/distribution-of-rx-drug-coverage/>).

²⁷ Peterson-Kaiser, Health System Tracker, “What are the recent and forecasted trends in prescription drug spending?” (https://www.healthsystemtracker.org/chart-collection/recent-forecasted-trends-prescription-drug-spending/#item-percent-of-total-rx-spending-by-oop-private-insurance-and-medicare_nhe-2017).

that consumers and their physician-agents will be relatively insensitive to the prices of prescription drug therapies.²⁸

17. The lack of price sensitivity on the part of physicians and patients due to insurance has had two important consequences for the demand for prescription drugs: (1) patients will tend to consume more prescription drugs than they would absent coverage and (2) there is less (if the consumer pays coinsurance, for example) or no (if the consumer has fixed dollar copayments or has exceeded her out-of-pocket maximum) incentive to choose a lower-priced product. In economic jargon, these effects together are known as moral hazard.²⁹ The effect of moral hazard is to increase health care spending, while raising the potential for wasted resources.

B. Regulatory Oversight of Pharmaceuticals

18. The Food and Drug Administration (FDA) oversees the availability of pharmaceutical products in the U.S. market. Under the Federal Food, Drug, and Cosmetic Act (FDCA), the FDA has a limited role in regulation of the promotion of prescription drug products.

19. Since 1962, the FDCA and related regulations have required sponsors of new drug products to present scientific evidence of both efficacy and safety before a new product can be marketed.³⁰

²⁸ J. Newhouse and the Insurance Experiment Group, *Free for All? Lessons from the RAND Health Insurance Experiment*, Cambridge, MA: Harvard University Press, 1993.

²⁹ J. Bhattacharya, T. Hyde, and P. Tu, *Health Economics*, New York: Palgrave MacMillan, 2014, pp. 204-05.

³⁰ FDA, "Significant Dates in U.S. Food and Drug Law History" (<http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm>)

20. By regulation, prescription drug labels indicate the diseases, conditions, and/or patients for which the sponsor has presented scientifically-required evidence to the FDA.³¹

21. FDA regulations specify that promotional materials may only make claims that are supported by scientific evidence (i.e., supported by studies meeting scientific standards) and they may not be false or misleading. The same general requirements apply to both professional and consumer-oriented marketing.³²

22. FDA oversight of drug promotion is intended to ensure that physicians and consumers understand both the benefits and risks of a drug. FDA regulations call for “fair balance” in all promotional claims and materials. The risks as well as the benefits must be clearly identified, and risks must be given appropriate prominence.³³

C. Pharmaceutical Promotion: Tactics and Evidence of Impact

23. During at least the period relevant to this case (about 1995 to the present), pharmaceutical companies have employed a variety of promotional tactics for prescription drugs. These efforts may be directed at prescribers, patients or payers. Physician-oriented marketing efforts include visits or phone calls by pharmaceutical sales representatives to physicians (detailing), free samples, print advertising, sponsorship of medical education events and influencing treatment guidelines or algorithms. Direct-to-consumer (DTC) advertising of

³¹ See, for example, 21 C.F.R. §202.1(e)(4); 21 U.S.C. §355 (a)-(b); 21 C.F.R. §314.126, and 21 U.S.C. §355(d).

³² The category of professional marketing includes detailing, advertising in medical journals, the use of free samples, and sponsorship of meetings and events. Consumer-oriented marketing takes the forms of advertising in popular magazines, broadcast advertising on radio and television, and internet advertising.

³³ See, *e.g.*, 21 C.F.R. §202.1.

prescription drugs on television, radio, internet and in popular magazines has increased substantially over the past two decades, reaching \$6 billion in 2016.³⁴ Payor-oriented marketing includes seeking to influence formulary placement.³⁵

24. Despite the numerous forms of pharmaceutical marketing, marketing to physicians and other professionals remains the largest component of pharmaceutical marketing. In total, marketing to physicians grew from \$15.6 billion in 1997 to \$20.3 billion in 2016.³⁶ The 2016 figure includes \$5.6 billion for detailing, \$13.5 billion in free samples, and \$979 million in “transfers of value” to physicians (e.g., speaking fees, meals) and \$59 million for unbranded educational campaigns. Because of its economic importance as the leading category of promotional spending, promotion to physicians is the most studied form of pharmaceutical promotion. Thus, I devote special attention in this section to the role of promotion to physicians and its impact on prescribing.

25. Pharmaceutical marketing campaigns may directly reach an individual physician, but they also have indirect effects through professional networks and peer interactions (see Figure 1 below).³⁷ As plaintiffs’ marketing expert Dr. Perri states, peer-to-peer marketing acts as a

³⁴ *Ibid.* Also see Rosenthal, *et al.* (2002), *op. cit.*

³⁵ According to Plaintiffs’ pharmaceutical marketing expert, Dr. Perri, “The record in this case certainly supports the proposition that Defendants planned and worked diligently with multiple target audiences, including TPPs and PBMs to ensure and maintain formulary coverage for the opioids they marketed.” Expert Report of Matthew Perri, III, in this matter, March 25, 2019 (hereafter “Perri Report”), ¶ 40.

³⁶ L.M. Schwartz and S. Woloshin, “Medical Marketing in the United States, 1997-2016,” *Journal of the American Medical Association*, 321(1), 2019, pp. 80-96.

³⁷ Peer networks may include other physicians in a group practice, with admitting privileges at the same hospital or those with whom a physician trained. Practice pattern variation analysis and physician surveys have confirmed the flow of information through these networks. See A. Chandra, D. Cutler, and Z. Song, “Who Ordered That? The Economics of Treatment Choices in Medical Care,” in *Handbook of Health Economics*, Volume 2, eds. M. Pauly, T. McGuire, and P. Barros, Waltham, MA: Elsevier, Chapter 6.3, at p. 418.

form of contagion. “In sum, [Key Opinion Leaders] KOLs are used to “infect” other prescribers with favorable opinions regarding a company’s drug.”³⁸

26. Moreover, in some product areas including opioids, “unbranded” promotional efforts may also affect product sales.³⁹ For example, pharmaceutical companies may sponsor or work with professional or consumer advocacy groups to issue new clinical guidelines or develop consensus about medical phenomena. In this matter, for example, it is alleged that the manufacturer Defendants sponsored the American Pain Society and American Association of Pain Medicine efforts to increase the use of opioids to control pain and to promote new guidelines for state medical boards to support more aggressive use of opioids.⁴⁰ More examples of unbranded promotion by Defendants are identified and discussed in the next section.

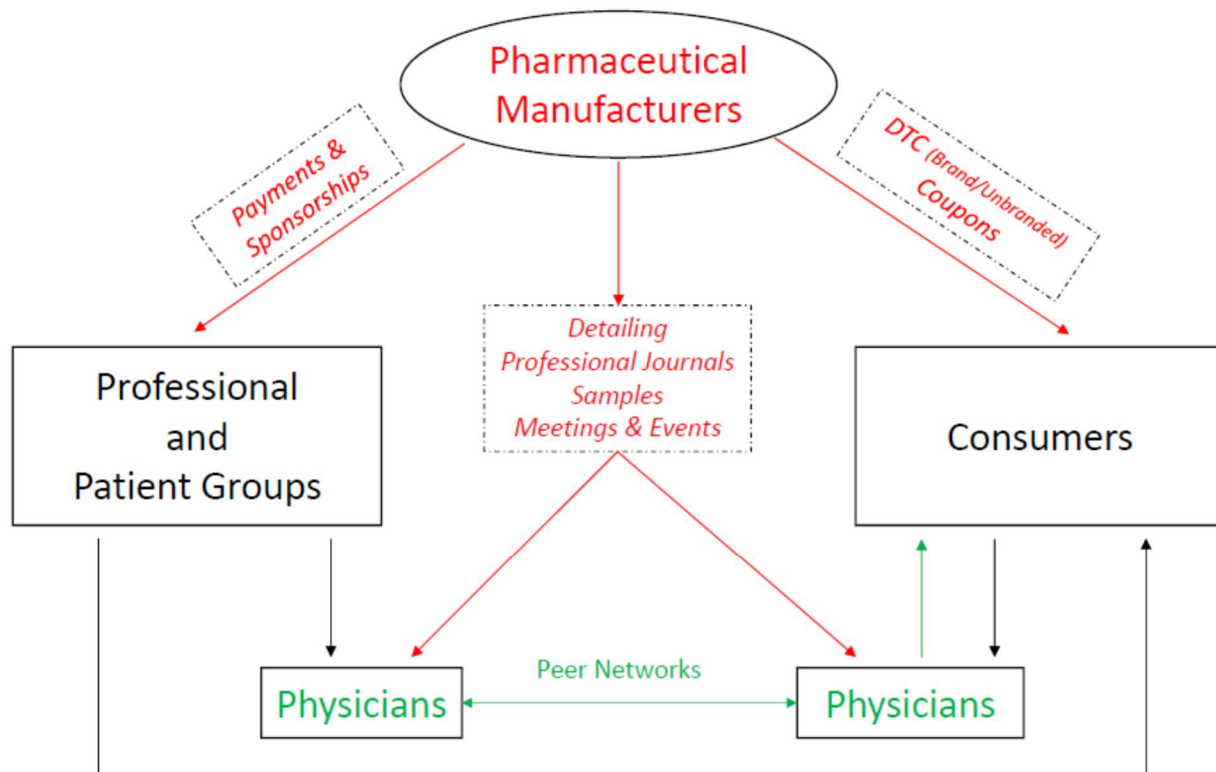
³⁸ Perri Report, ¶ 69.

³⁹ T. Alves, *et al.*, “Unbranded advertising of prescription medicines to the public by pharmaceutical companies,” *Cochrane Database of Systematic Reviews*, Issue 7, 2017, Art. No. CD012699.

⁴⁰ Dr. Perri concludes that Defendants’ payments to professional and patient advocacy groups served a marketing purpose. For example, he notes: “Advocacy support by Defendants also was extended to groups like the Joint Commission on Accreditation of Hospitals (JCAHO) and the Federation of State Medical Boards (FSMB) both of which distributed guidelines or standards for opioid use.” (Perri, ¶¶ 71).

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FIGURE 1
PROMOTION ECOSYSTEM



27. As Figure 1 illustrates, physicians do not need to be detailed directly or otherwise exposed to company marketing materials individually to be influenced due to peer networks and the role of consumer demand. A study by Coleman concluded that there are two separate diffusion processes going on among physicians.⁴¹ “Isolated” physicians are influenced only by “external” influences, such as journal articles and contacts with detail people. But the vast majority of doctors are integrated into professional and social networks. For this latter group,

⁴¹ J.S. Coleman, E. Katz, and H. Menzel, *Medical Innovation: A Diffusion Study*, Indianapolis: Bobbs-Merrill, 1996.

external influences affect a few of them, referred to as “early adopters,” and they go on to “infect” others.

28. Interest in the influence of pharmaceutical companies on physician decision making has motivated numerous studies in the clinical literature on the impact of promotion on physician beliefs, knowledge and self-reported behavior.⁴² I highlight a few of the most salient examples of this extensive literature.

29. Avorn, Chen and Hartley⁴³ analyzed physician beliefs about the sources of influence on their prescribing as well as indirect evidence of the true source of physician information. Physicians were asked to report their beliefs about the pharmacologic effects of two classes of drugs where the scientific evidence had clearly shown little or no benefit while the manufacturers had advertised heavily to promote the products as superior to the therapeutic alternatives. Although physicians reported that commercial sources of information had little influence on their prescribing habits, the majority held beliefs about the two classes of drugs that were consistent with the detailing message and at odds with the scientific evidence. Importantly, the findings show not only that physicians can be influenced by false product claims, but also that asking physicians whether their views on the benefits and risks of a

⁴² E. Clayton, “’Tis Always the Season for Giving,” CALPIRG Report, September 2004, pp. 1-9; Editorial Staff, “Pharmaceutical Marketing to Physicians: Free Gifts Carry a High Price,” *American Medical News*, June 10, 2002; A. Wazana, “Physicians and the Pharmaceutical Industry,” *Journal of the American Medical Association*, 283(3), January 19, 2000, pp. 373-80; A. Fugh-Berman, “The Corporate Coauthor,” *Journal of General Internal Medicine*, 20(6), 2005, pp. 546-48; P. Manchanda and E. Honka, “The effects and role of direct-to-physician marketing in the pharmaceutical industry: an integrative review,” *Yale Journal of Health Policy Law & Ethics*, 5, 2005, pp. 785-812; C. DeJong, et al., “Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries,” *JAMA Internal Medicine*, 176(8), 2016, pp. 1114-22.

⁴³ J. Avorn, M. Chen, and R. Hartley, “Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians,” *American Journal of Medicine*, 73(1), 1982, pp. 4-8.

particular treatment were shaped by pharmaceutical sales representatives or other promotional tactics is a poor method of identifying whether or not promotion is persuasive. This is hardly surprising and further support for the empirical methods preferentially used by economists, which follow the logic of “revealed preference” (making inferences based on what subjects do, rather than what they say).⁴⁴

30. While the Avorn, Chen and Hartley study suggests that physicians do not recognize their own vulnerability to commercial influences, physicians do generally perceive pharmaceutical marketing to be effective when surveyed.⁴⁵ However, they deny that gifts and payments could influence their prescribing behavior;⁴⁶ indeed, receipt of gifts from the industry was associated with the belief that pharmaceutical representatives have no impact on prescribing behavior.⁴⁷

31. Numerous studies have examined the association between specific types of physician behavior and the extent of contact with pharmaceutical representatives, receipt of free samples, attendance of company-sponsored events, or receipt of gifts. These studies have

⁴⁴ M. Bertrand and S. Mullainathan, “Do people mean what they say? Implications for subjective survey data,” *American Economic Review*, 91(2), 2001, pp. 67-72.

⁴⁵ Dr. Perri also concludes that: “Physicians may not be able to easily discriminate between promotional information and scientific evidence.” He cites: F. Fickweiler, W. Fickweiler, and E. Urbach, “Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians’ attitudes and prescribing habits: A systematic review,” *BMJ Open*, 7, 2017, e016408. Perri Report, ¶ 62.

⁴⁶ A. Wazana, *op. cit.* See also J. Dana and G. Loewenstein, “A Social Science Perspective on Gifts to Physicians From Industry,” *Journal of the American Medical Association*, 290(2), 2003, pp. 252-55. Physician denial of the influence of industry communication, samples and gifts (including free medical education) may be understood in the context of extensive findings from behavioral psychology regarding unintentional and subconscious biases.

⁴⁷ W. Sandberg *et al.*, “The Effect of Educational Gifts from Pharmaceutical Firms on Medical Students’ Recall of Company Names or Products,” *Academic Medicine*, 72(10), 1997, pp. 916-18; B. Hodges, “Interactions with the Pharmaceutical Industry: Experiences and Attitudes of Psychiatry Residents, Interns and Clerks,” *Canadian Medical Association Journal*, 153(5), 1995, pp. 553-59.

demonstrated a positive effect of pharmaceutical promotion and company-sponsored continuing medical education (CME) on the following:

- Formulary requests;⁴⁸
- Prescribing of new drugs vs. older, generic products;⁴⁹ and
- Prescribing of the specific product that was being promoted.⁵⁰

32. In addition to studies in the clinical literature, which are typically descriptive, a relatively rich empirical literature in economics and marketing has developed in recent decades on quantifying the the impact of promotion on pharmaceutical sales. These studies estimate the responsiveness of product sales to own and competitor marketing expenditures. In most cases, the results are expressed as elasticities, which are defined as the ratio of the percentage change in unit sales for a given percentage change in promotion. For example, if a study found an elasticity of promotion of 0.70, that would indicate that a 10% increase in promotion would increase unit sales by 7%. Estimates vary across studies, in part due to differences in the classes of drugs studied, the product lifecycle, time periods, and the research designs implemented.

⁴⁸ M. Chren and C. Landefeld, "Physicians' Behavior and Their Interactions With Drug Companies: A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary," *Journal of the American Medical Association*, 271(19), 1994, pp. 684-89. G. Spurling, *et al.*, "Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review," *PLoS Medicine*, 7(10), 2010, e1000352 (finding "With rare exceptions, studies of exposure to information provided directly by pharmaceutical companies have found associations with higher prescribing frequency, higher costs, or lower prescribing quality or have not found significant associations.")

⁴⁹ M. Peay and E. Peay, "The Role of Commercial Sources in the Adoption of a New Drug," *Social Science & Medicine*, 26(12), 1988, pp. 1183-89.

⁵⁰ *Ibid.*

33. There is notable consensus, however, that promotional effects are long-lived. This concept is measured in the literature by examining the relationship between sales and the stock of promotion: the cumulative amount of promotion, subject to discounting over time. Research suggests that depreciation rates for promotional stocks are close to zero, which means that the effects of past promotion continue almost indefinitely into the future. One possible reason for these long-lived effects is habit formation, both on the part of doctors and patients. Representative findings from the economics and marketing literature include the following:

- A study by Azoulay investigated the impact of both pharmaceutical company promotional efforts and scientific publications on prescribing behavior in the case of anti-ulcer drugs. He finds a significant effect on sales for both types of communication, with promotional efforts (specifically detailing flows) having a larger effect.⁵¹ Detailing elasticities of demand for the four drugs studied range from approximately 0.7 to 1.2.⁵²
- Berndt, *et al.*⁵³ distinguish between “industry expanding” and “rivalrous” marketing efforts, and find that for anti-ulcer medications, cumulative spending (i.e., stocks) on both medical journal and physician detailing increases own-brand sales. They also find

⁵¹ P. Azoulay, “Do Pharmaceutical Sales Respond to Scientific Evidence?” *Journal of Economics and Management Strategy*, 11(4), 2002, pp. 551-94. It should be noted that because many scientific studies of prescription drugs are funded by the manufacturer the separation between promotion and scientific evidence that Azoulay assumes may not, in reality, exist. L. Friedman and E. Richter, “Relationship Between Conflicts of Interest and Research Results,” *Journal of General Internal Medicine*, 19(1), 2004, pp. 51-56.

⁵² The elasticity measures the size of the proportional increase in sales relative to the size of the proportional increase in promotional spending inducing that sales increase. The elasticity estimates are found to vary with number of therapeutic competitors in the market.

⁵³ E. Berndt, *et al.*, “Information, Marketing and Pricing in the U.S. Antiulcer Drug Market,” *American Economic Review*, 85(2), 1995, pp. 100-05.

that market-expanding promotion (*e.g.*, marketing that increases awareness of the existence of a new use for a drug) depreciates very slowly. The paper contains estimates of marketing elasticities of 0.5 and 0.2 at the class level for the stock of spending on detailing and professional journal advertising, respectively. They also report that the impact of total class marketing efforts on total class sales is positive, and generally (but not always) declines with the number of products on the market.

- Rizzo⁵⁴ reports that for antihypertensive drugs, both stocks and flows of detailing expenditures decrease the price elasticity of demand over time because promotional expenditures create greater brand loyalty. Thus, in addition to increasing the sales of marketed drugs, promotion may also increase perceived product differentiation, market power, and prices.

34. In the marketing literature, scholars have tended to focus on how manufacturers target promotional spending – examining questions about the effectiveness of detailing the same physicians repeatedly vs. spreading resources across a larger number of physicians. I summarize findings from some examples of this literature as follows:

- Manchanda and Chintagunta⁵⁵ use physician-specific data on detailing visits and prescriptions to examine the importance of the distribution of marketing efforts across targets. They find that detailing has a significant positive impact on the number of

⁵⁴ J. Rizzo, "Advertising and Competition in the Ethical Pharmaceutical Industry: The Case of Antihypertensive Drugs," *Journal of Law and Economics*, 42(1), 1999, pp. 89-116.

⁵⁵ P. Manchanda and P. Chintagunta, "Responsiveness of Physician Prescription Behavior to Salesforce Effort: An Individual Level Analysis," *Marketing Letters*, 15(2-3), 2004, pp. 129-45.

prescriptions written for a drug by the physician, that this marginal impact increases when free product samples are also provided to the physician, and that for the majority of physicians in their sample, diminishing (though still positive) returns to detailing had already set in.

- Gonul, *et al.*⁵⁶ use similar data and a similar analytic approach to examine the impact of price, patient insurance, detailing and samples on brand choice within a specific therapeutic class. The authors find that both detailing and free samples increase the probability that a drug is prescribed.
- Datta and Dave⁵⁷ analyze effects of detailing and sampling of a branded drug indicated for the treatment of herpes infections, using data on 149,000 individual physicians over a 24-month period. They find that detailing of the drug significantly increased its prescribing among sample physicians, while decreasing prescribing of other brand drugs that treat the same condition.
- Mizik and Jacobson⁵⁸ study detailing of three drugs to a sample of 74,075 individual physicians over a 24-month period. For all three drugs, both detailing visits and free samples had positive and statistically significant effects on prescribing levels, although the magnitudes of estimated effects were relatively modest.

⁵⁶ F. Gönül, *et al.*, "Promotion of Prescription Drugs and Its Impact on Physicians' Choice Behavior," *Journal of Marketing*, 65(3), 2001, pp. 79-90.

⁵⁷ A. Datta and D. Dave, "Effects of Physician-directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence," *Health Economics*, 26(4), 2017, pp. 450-68.

⁵⁸ N. Mizik and R. Jacobson, "Are Physicians 'Easy Marks'? Quantifying the Effects of Detailing and Sampling on New Prescriptions," *Management Science*, 50(12), 2004, pp. 1714-15.

35. Promotional efforts by drug manufacturers have also been shown to affect physician decision making regarding off-label uses. Indeed, the widespread nature of off-label use, with and without scientific evidence to support use suggests that there are ample incentives for manufacturers to engage in these tactics.⁵⁹ In one study of this phenomenon, Steinman, *et al.* fielded a survey of physicians who were visited by drug representatives who delivered promotional messages that were classified as approved (on-label), unapproved (off-label) or a combination of both.⁶⁰ The physicians were then asked about whether those messages, along with other attributes of the detailing visit, would influence their future decisions of whether to prescribe or recommend the drug for the purpose described by the pharmaceutical representative. The authors found statistically similar impacts of approved messages and unapproved messages on physicians' intentions to prescribe.⁶¹

36. Larkin, *et al.*,⁶² also demonstrated that pharmaceutical marketing causes off-label use. The paper took advantage of a natural experiment among 23 academic medical centers (AMCs), of which some introduced policies restricting detailing, and some did not. Of the 23 AMCs, 15 centers introduced policies restricting detailing during the study period; these centers formed the intervention group. The remaining 8 AMCs did not have any change in policies during the study period and formed the control group. The study focused on 38 antidepressant and

⁵⁹ D. Radley, S. Finkelstein, and R. Stafford, "Off-label prescribing among office-based physicians," *Archives of Internal Medicine*, 166(9), 2006, pp. 1021-26.

⁶⁰ M. Steinman, *et al.*, "Characteristics and impact of drug detailing for gabapentin," *PLoS Medicine*, 4(4), 2007, pp. 743-51.

⁶¹ *Ibid.*, p. 743. In drawing inferences from this finding, the authors conclude "physicians reported similar increases in future prescribing or recommending of gabapentin after exposure to approved or unapproved messages." p. 747.

⁶² I. Larkin, D. Ang, J. Avorn, and A. Kesselheim, "Restrictions on Pharmaceutical Detailing Reduced Off-label Prescribing of Antidepressants and Antipsychotics in Children," *Health Affairs*, 33(6), 2014, pp. 1014-23.

antipsychotic drugs that were prescribed for children. The authors found that eliminating detailing caused prescriptions for off-label use of promoted drugs to fall by 11 percent, relative to the control group, “consistent with the ongoing presence of off-label marketing.”⁶³ While reductions in on-label uses of promoted drugs were greater (34%), this finding does not necessarily suggest that on-label marketing is more effective because there is no measure here of the relative intensity of on- vs. off-label marketing efforts pre-intervention.

37. I conclude that the observed importance of promotional activities in the pharmaceutical industry and the findings of rigorous empirical analyses relating promotion to sales establish a causal link between pharmaceutical promotion and sales. Empirical research also demonstrates that promotion can increase off-label as well as approved uses of products.

38. Furthermore, I find that physicians can be misled by commercial messages that are inconsistent with scientific evidence. This conclusion is supported by direct ascertainment of physician beliefs⁶⁴ and by previous analyses of successful marketing campaigns for unapproved uses of prescription drugs.⁶⁵ To the extent that information is false, incomplete or misleading, physicians can be misled.

⁶³ *Ibid.*, p. 1014.

⁶⁴ J. Avorn, M. Chen, and R. Hartley, “Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians,” *American Journal of Medicine*, 73(1), 1982, pp. 4-8.

⁶⁵ Steinman, *et al.*, *op. cit.*

VII. PROMOTION AND OPIOIDS

A. Published Research

39. The opioid epidemic has spurred both investigative journalism and academic research into the causes of increased opioid prescribing. Some of this work focuses on the promotional activities of manufacturers including the Defendants. For example, Zee,⁶⁶ writing on Purdue's marketing efforts for oxycontin notes the following: "When Purdue Pharma introduced Oxy-Contin in 1996, it was aggressively marketed and highly promoted. Sales grew from \$48 million in 1996 to almost \$1.1 billion in 2000." Zee identifies a number of other promotional activities that contributed to the increase in sales, despite comparable efficacy to other products available (e.g., oxycodone). For example, he notes that Purdue conducted more than 40 national pain management and speaker training conferences from 1996 to 2001 and funded more than 20,000 pain-related educational programs.

40. A recent study by Hadland et al.⁶⁷ found that between 2013 and 2015 over 375 thousand non-research payments involving a marketed opioid product were made to over 68 thousand US physicians (representing 1 in 12 active physicians) totaling over \$46 million. In a subsequent article, Hadland et al.⁶⁸ find that among physicians who prescribed to Part D enrollees, those physicians who received payments in 2014 had increased prescribing in 2015 compared with physicians who received no payments.

⁶⁶ A. Van Zee, "The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy," *American Journal of Public Health*, 99(2), 2009, pp. 221-27.

⁶⁷ S.E. Hadland, M.S. Kreiger and B.D. Marshall, "Industry Payments to Physicians for Opioid Products, 2013-2015," *American Journal of Public Health*, 107(9), 2017, pp. 1493-95.

⁶⁸ S.E. Hadland, et al., "Association of Pharmaceutical Industry Marketing of Opioid Products to Physicians with Subsequent Opioid Prescribing," *JAMA Network Open*, 2(1), 2019, p. e186007.

41. Similarly, the New York State Health Foundation⁶⁹ found that “roughly 1 in 10 physicians who prescribe opioids received a payment, and physicians who prescribe more opioids got more opioid-related payments. Even though most of these payments are relatively small, the data show clear links between payments from manufacturers and increased opioid prescribing.”

42. While these latter two studies demonstrate the magnitude of industry “transfers of value” to physicians related to opioid prescribing, they do not attempt to identify a causal effect of marketing on sales. As the authors acknowledge, the contemporaneous association between payments and prescriptions may be caused by industry targeting of payments to high prescribers.

B. The Defendants’ Own Materials Recognize the Effects of Promotion on Opioid Sales

43. Given the enormous profits that manufacturers can earn on pharmaceutical sales and the billions of dollars that are devoted to marketing, it is not surprising that manufacturers engage in systematically tracking promotional efforts.⁷⁰ As noted above for the industry as a

⁶⁹ New York State Health Foundation, “Follow the Money: Pharmaceutical Manufacturer Payments and Opioid Prescribing Patterns in New York State,” June 2018 (<https://nyshealthfoundation.org/wp-content/uploads/2018/06/following-the-money-pharmaceutical-payments-opioid-prescribing-june-2018.pdf>).

⁷⁰ For examples:

- Allergan has analyzed profitability of its Adherence Program (ALLERGAN_MDL_00221533 at 534-543; ALLERGAN_MDL_00450170 at 176-185).
- Endo has analyzed the profitability of specific programs such as promotional speaker programs (EPI001514810 at slide 35); Instant Savings Card programs (EPI001514810 at slide 52; ENDO00563922 at 923-936 and 945); as well as profitability of general detailing and marketing activities (ENDO-CHI_LIT-00214471 at slides 8-66).
- Janssen has analyzed the profitability of detailing (JAN-MS-00309600 at slides 7-9; JAN-MS-00314171), as well as for specific marketing programs such as E-marketing, Health Resource Newsletter, Sample Voucher Program, Visiting Professor program, Pain Experts Fellowship Program, and Desk Calendar (JAN-MS-00494171 at slides 12-16, 47, and 54).

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whole, documents obtained through discovery in this matter suggest that detailing is the largest category of promotional spending.⁷¹ Unbranded promotion, which includes “help-seeking” advertisements as well as the funding of research, lobbying groups, and interest groups can also affect sales,⁷² often with classwide effects.

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- Mallinckrodt has analyzed how to maximize profitability for its detailing efforts (MNK-T1_0000947739 at 742-743).
 - Purdue has analyzed the profitability of its biggest promotional for OxyContin, presentations to high decile HCPs and the OxyContin Savings Card Program (PPLP003449398 at 402), repeatedly and across prescriber specialties (PPLPC012000395903 at slides 14-22; PPLPC025000145757 slides 22-26 and 40-49; PPLPC025000147119 at slides 6-17; PPLPC025000148523 at slides 8-22).
 - Teva has analyzed the extent that different promotional activities drive new prescriptions as well as these programs profitability across time (TEV_FE00114124 at 134-140; TEV_FE00114319 at 327-328; TEVA_MDL_A_00556014 at slides 5-16; TEVA_MDL_A_00755335 at 339-346 and 358-359; TEVA_MDL_A_00886031 at slides 5-6, 19, 35, and 56; TEVA_MDL_A_01205575 at slide 3).

⁷¹ For examples:

- From the years 1995-2002, 2005-2006, 2008-2009, and 2011-2014, Purdue allocated 86.5% of their OxyContin marketing budget to detailing: PKY181266046 at 047 and 049; PKY183222319 at 416 and 417; PKY180246682 at 914; SHC-000001119 at 162; PKY181678793 at 844; CHI_000169914 at 962; PPLP003420958 at 989; PPLP003420990 at 034 and 035; PDD9273201211 at 223 and 224; PDD9273201289 at 309 and 310; PPLP003420538 at 560 and 561; PPLP003421452 at 470; PPLP004134382 at 430.
- From the years 2010-2014, Mallinckrodt allocated 73.5% of their Exalgo marketing budget to detailing: MNK-T1_0000929284; MNK-T1_0000708777 at 968; MNK-T1_0000913808.
- From the years 2009-2012, Endo allocated 69.3% of their Opana marketing budget to detailing: EPI001466339 at slide 76; ENDO-CHI_LIT-00439415 at slide 55.

⁷² For examples:

- Purdue made payments to Partners Against Pain part of OxyContin according to annual marketing plans (“2010 Budget Submission” (2009), PDD9273201211 at 224; “OxyContin Annual Marketing Plan” (2014), PPLP003425040 at 062). Purdue also funded “the very first meeting of the AAPM/APS/ASAM leadership [...] to begin the collaboration that eventually led to the Consensus statement on definitions of pain and addiction” and the Federation of State Medical Boards (FSMB) to create documents such as “Responsible Opioid Prescribing: A Physician’s Guide” to promote the use of opioid analgesics (PPLP003477086 at 109).
- Endo established the National Initiative on Pain Control (NIPC) in 2001. Between 2003-2012 Endo paid the NIPC tens of millions (MDL_KP360_000000002). From 1999-2012 Endo reported to have paid groups including the American Pain Foundation (APF) (\$5.94 million), American Academy of Pain Medicine (AAPM) (\$1.31 million), American Pain Society (APS) (\$4.47 million), American Geriatrics Society (AGS) (\$0.34 million), Joint Commission on Accreditation (formerly JCAHO) (\$0.75 million), and the Federation of State Medical Boards (FSMB) (\$0.37 million) (ENDO-OR-CID-00718227 at sheet “All Payments”).
- Janssen made payments to the American Academy of Pain Management (AAPM), the American Pain Foundation (APF), the American Pain Society (APS), the American Geriatric Society (AGS), and others (JAN-

44. Discovery materials produced in this matter show that the Defendants tracked promotional effectiveness and used data to target their salesforce, messaging and other resources to increase sales. Promotional strategy documents often feature estimates of the return on investment (ROI) for individual tactics or messages. The ROI, expressed as a multiple or percentage, provides an indication of the dollars of profit earned per dollar of marketing expenditure.

45. The ROI for detailing visits found in documents is consistently high for Defendant promotion of brand opioid drugs in this case. Examples include Fentora (Teva) for which some messages had ROIs of 500% in 2014, 136% in 2013, 168% in 2012, and 462% in 2010⁷³; Duragesic (Janssen) where the manufacturer's analysis showed that detailing not only resulted in new prescriptions in the current period but also in future time periods upwards of 11 months after the detail⁷⁴; and Exalgo (Mallinckrodt) where documents show that the manufacturer fine-tuned detailing contacts based on profitability calculations.⁷⁵ Purdue similarly reported ROIs as high as 370% for detailing OxyContin to high decile healthcare providers.⁷⁶

MS-00264548 at Sheet1). Janssen's payments to the National Pain Education Council (NPEC) were part of a strategy to increase prescriptions by "Strategy: Leveraging Functionality to differentiate DURAGESIC as the optimal Long Acting Opioid" (DURAGESIC The Tipping Point, 2003 Tactical Plan" (2003), JAN-MS-00494171 at slide 35.)

⁷³ "Fentora Marketing Mix Analysis Impact Assessment Findings Review" (2014), TEVA_MDL_A_02767666 at 673; "2014 Teva Portfolio Mix Planning" (2013), TEVA_MDL_A_00886031 at slide 19; Fentora – Promotional Response Study" (2010), TEVA_MDL_A_00556014 at slide 12.

⁷⁴ "Strike Force Sales Rep Alignment: Feasibility Analysis from ROI Perspective" (2003), JAN-MS-00309600 at slide 8.

⁷⁵ "Exalgo Detail ROI Analysis" (2013), MNK-T1_0000947739 at 742-743.

⁷⁶ "OxyContin Tablets Promotional Planning" (2013), PPLP003449398 at 402.

46. The Defendants calculated positive ROIs for non-detailing promotional activities as well. For example, in 2009 Allergan found a positive ROI for a prescription adherence program used in its marketing of Kadian that actually grew with time from 9.8:1 after 6 months to 15.9:1 after 12 months.⁷⁷ Endo similarly reported a positive ROI that increased with time for promotional speaker programs for Opana ER, eventually reaching nearly 200% at the end of the 28 week long study.⁷⁸ Janssen reported ROIs for a diverse set of non-detailing promotional activities for Duragesic in 2002, including e-marketing (2:1), a Health Resource Newsletter (2:1), sample voucher program (13:1), its investments in National Pain Education Council (NPEC), and Regional Advisory Boards.⁷⁹

47. Other forms of promotion have also been reported for opioids, including practices that have been the subject of prior litigation. In 2007, Purdue Pharma LLC acknowledged in a guilty plea that certain employees “with the intent to defraud or mislead, marketed and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications.”⁸⁰ Another example, currently in trial, concerns executives for Insys Therapeutics who are charged with paying kickbacks, wire fraud, mail fraud and racketeering conspiracy.⁸¹ Under questioning by prosecutors, former Insys CEO Michael Babich, who pleaded guilty to conspiracy and fraud, “reviewed dozens of Insys e-mails that have been entered into evidence. He said high-ranking executives at Insys painstakingly

⁷⁷ “Kadian Patient Persistency and In-Class Case Study” (2009), ALLERGAN_MDL_00450170 at 176-78 and 184-85.

⁷⁸ “2009 OPANA Brand Plan” (2008), EPI001514810 at slide 35.

⁷⁹ “DURAGESIC The Tipping Point” (2002), JAN-MS-00494171 at slides 12-58.

⁸⁰ US v. Purdue Frederick Co., Inc., 495 F. Supp. 2d 569 (W.D. Va. 2007).

⁸¹ U.S. v. Kapoor, 16-cr-10343, U.S. District Court, District of Massachusetts.

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identified doctors around the country who had a history of prescribing opioids, then wooed those physicians and funneled what he called bribes to them through a sham speakers program.”⁸² Further, according to Babich “the company’s budget included sales bonuses tied to the dosage of the Subsys prescriptions. A prescription for the 1,600-microgram dose would earn a sales person a bonus of \$1,830.”⁸³

48. Discovery materials underscore that opioid pharmaceutical marketing efforts are national in scope. In particular, marketing messages are developed for the U.S. as a whole and disseminated through regional salesforces.⁸⁴

VIII. ECONOMETRIC ANALYSIS – DIRECT APPROACH

49. As noted above, I use two analytic approaches to quantify the impact of promotion on the the number of MMEs of opioids sold over the damage period: a “direct” method (in that the method models the impact of a particular mechanism, promotion, on sales) and an “indirect” method (in that the method permits an inference that a remaining mechanism, promotion, was

⁸² J. Saltzman, “In rap video, Insys opioid salesmen boasted of their prowess,” *Boston Globe*, February 13, 2019 (<https://www.bostonglobe.com/business/2019/02/13/rap-video-opioid-salesmen-boasted-their-prowess/YsPTTbiDYDq1ZlpEtobmXL/story.html>).

⁸³ J. Lawrence, “Sales Team Rap Video Adds to John Kapoor’s Woes at Opioid Trial,” *Bloomberg*, January 13, 2019 (<https://www.bloomberg.com/news/articles/2019-02-13/opioid-rap-video-adding-to-john-kapoor-s-woes-at-insys-trial>).

⁸⁴ See deposition testimony given in this matter by Defendants:

- Deposition of Julie Snyder, Allergan (November 2, 2018), 271:5-24; 272:1-3.
- Deposition of Ronald Perry Wickline, Endo Labs (November 13, 2018), 197:6-25.
- Deposition of Kimberly Deem-Eshleman, Janssen (November 15, 2018) 55:9-15.
- Deposition of Kimberly Deem-Eshleman, Janssen (November 15, 2018) 129:1-15.
- Deposition of Sally Riddle, Purdue (December 6, 2018), 49: 1-8; 50: 1-25; 51: 1-3.
- Deposition of Phil Cramer, Purdue (November 19, 2018) 177:23-25; 178:1-23.
- Deposition of John Hassler, Teva (November 16, 2018) 275:14-24; 276:1-5.
- Deposition of Kevin Vorderstrasse, Mallinckrodt (December 5, 2018) 269: 19-24; 270: 1-13.

causal). In this Section I describe and implement the direct approach to quantify the impact of the alleged misconduct. The direct estimation approach relates promotion to sales of opioids, using market-level data and a dynamic approach that I detail below. The indirect approach is described and implemented in Section IX.

50. In this section, I also present a descriptive analysis using the same market-level data that shows that dosing of opioids (measured as MMEs per prescription) escalated over time. Additional tables and charts are included in Attachment C and a technical discussion of the regression model, results and sensitivity tests are included in Attachment D.

A. Data Source and Trends

51. The primary data I use for the direct analysis come from the data tracking and consulting firm IQVIA. IQVIA maintains a number of data streams that capture information on sales, promotion, and other statistics by individual drug over time. These data are widely used by industry participants to monitor competitive conditions, track market growth, and identify strategic opportunities. They are also commonly used for academic research and economic analysis of pharmaceutical markets performed in the context of litigation such as this. The specific IQVIA products I incorporate into my econometric analysis include: the National Prescription Audit (NPA) and the Integrated Promotional Service (IPS). The NPA tracks sales of prescription drugs in retail outlets by drug by month including the retail transaction price (the amount actually paid to the pharmacy), the number of extended units (these are often pills or capsules but also include units of liquids) and the number of prescriptions. We convert extended units into MMEs using published conversion factors that are drug-specific. The IQVIA prescription database that is used to create the NPA draws from a representative sample of

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38,000 retail outlets, including chain, food/big box store, and independent pharmacies. IPS includes survey-based information from office-based practices about detailing and free samples by drug, as well as tracking of professional journal and direct-to-consumer advertising.

52. To set the stage for my analysis in this matter, I begin with a summary of data on sales and promotion for the opioid products at issue. In addition, a timeline of key events is included here for context.

53. Figure 2 shows monthly sales of the opioid drugs at issue in this matter, in both extended units and morphine milligram equivalents (MMEs).⁸⁵ These sales are national from 1993 through May 2018.⁸⁶ As can be seen in the figure below sales grew steadily until 2011 when sales peaked at more than [REDACTED] extended units and [REDACTED] MMEs per month. Since then sales in both extended units and MMEs have fallen steadily. Notably, the growth in opioid sales starts slowly in 1993 (with an average growth of [REDACTED] extended units per year) but accelerates substantially as it climbs towards its peak (the average increase in extended units between 2000 and 2011 was [REDACTED] per year). Opioid sales fell by an average of [REDACTED] extended units per year after 2011.⁸⁷

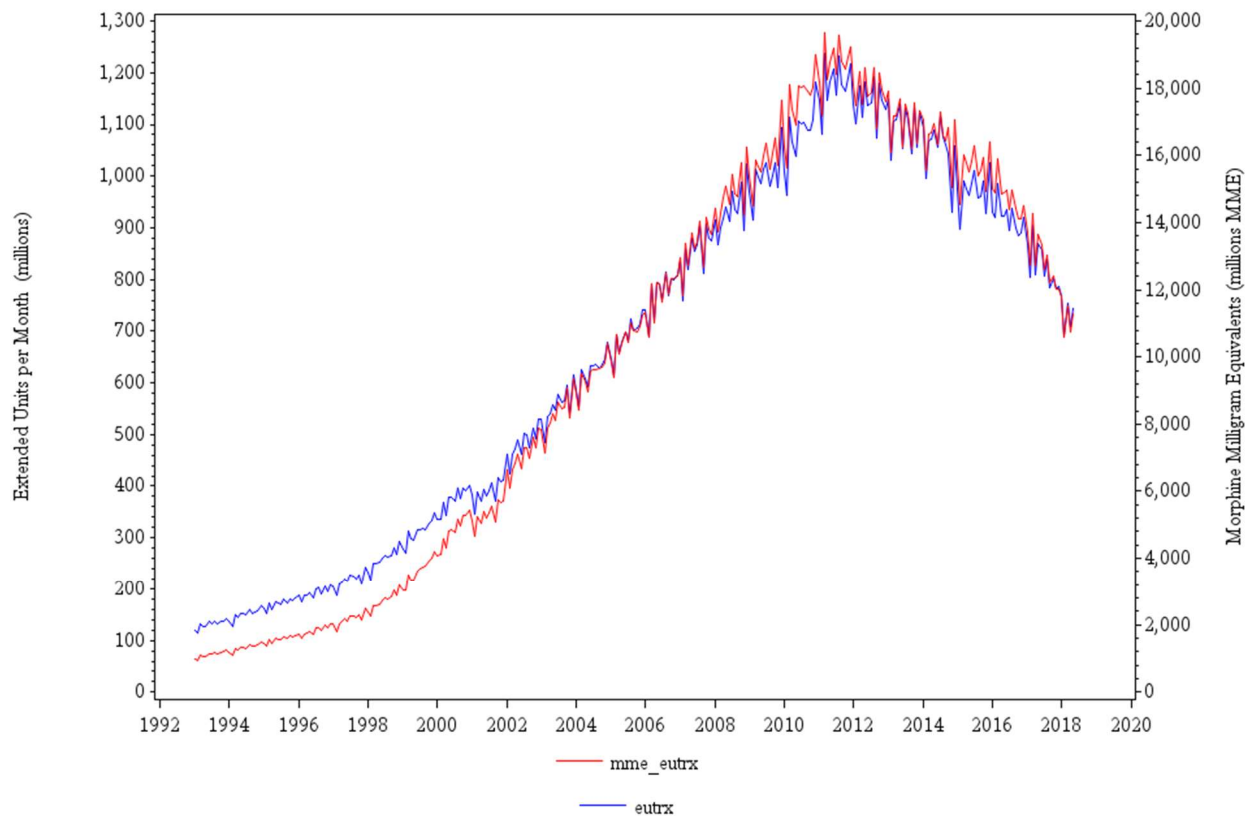
⁸⁵ Extended units are the units used in the IQVIA data to record dispensed amounts of the drug (e.g., tablets). MMEs convert extended units into morphine equivalents. MME conversion factors used in this report are from Centers for Disease Control, "Data Resources: Analyzing Prescription Data and Morphine Milligram Equivalents (MME)" (Excel spreadsheet available at <https://www.cdc.gov/drugoverdose/resources/data.html>) and Excellus Blue Cross Blue Shield, "Summary of Opioid POS for CY19" (https://www.excellusbcbs.com/wps/wcm/connect/4c541bc8-d8e2-41a1-9bba-83bbe1516ba6/Medicare+D+Formulary-Level+Cumulative+Opioid+and+Opioid++Buprenorphine+POS+Edits_03_01_2018.pdf?MOD=AJPERES&CACHEID=4c541bc8-d8e2-41a1-9bba-83bbe1516ba6).

⁸⁶ Note that while the plaintiffs intend to prove misconduct beginning in 1995, I use all the data available to me through IQVIA to estimate the most robust model possible. All but-for calculations begin in 1995.

⁸⁷ Based on calculations using IQVIA NPA, ARCOS, and CDC data, as detailed in Attachment D.

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FIGURE 2
SALES OF OPIOID DRUGS IN EXTENDED UNITS AND MMEs, 1993-2018

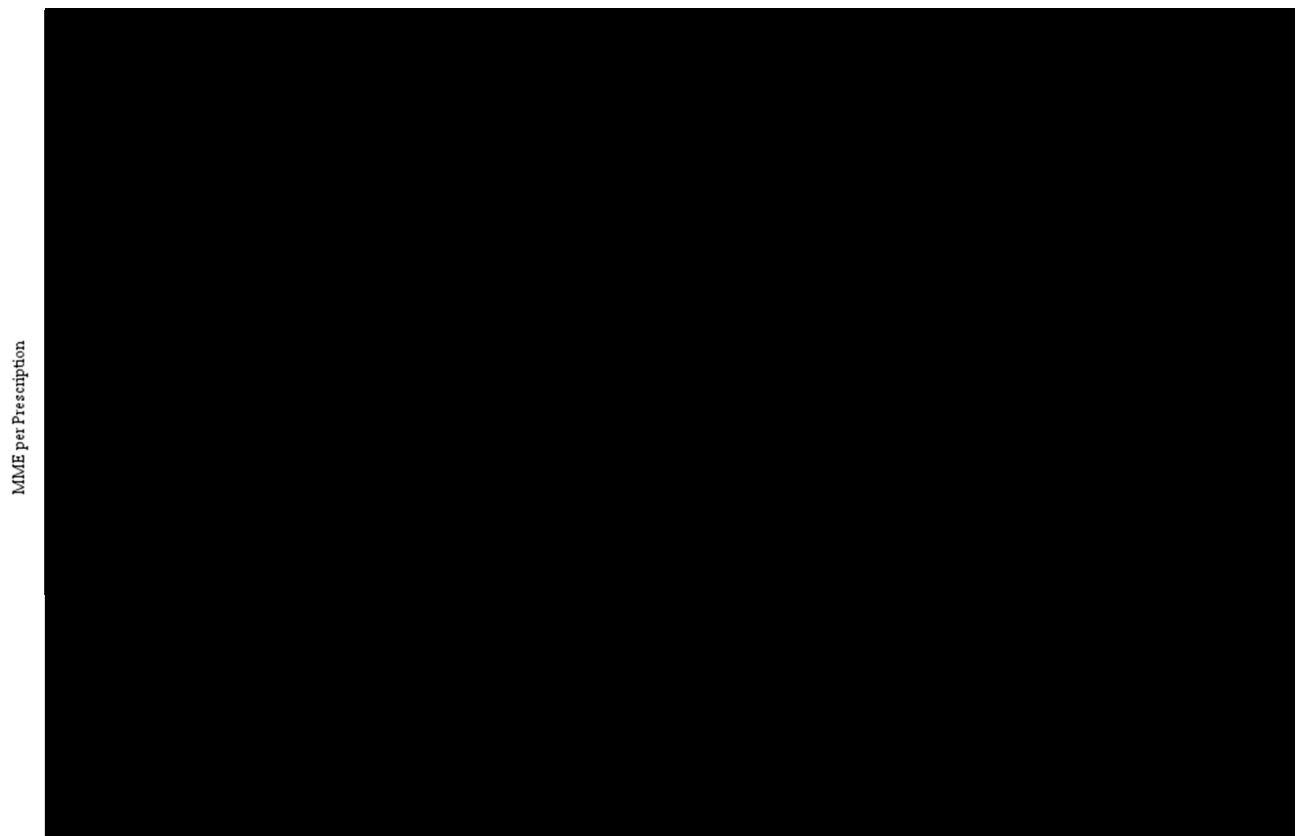


Source: IQVIA, NPA, ARCOS, CDC.

54. Figure 3 shows the trend in MMEs per prescription for the same group of opioid drugs. The figure demonstrates that dosing in MMEs increased over time in a similar pattern to overall sales, although the timing of its peak was somewhat later/earlier than the peak number of MMEs. These data show that patients receiving opioid prescriptions took home larger doses over time. The average dose per prescription [REDACTED] from 1993 to its peak in the 2010s.

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FIGURE 3
MMEs PER PRESCRIPTION, ALL OPIOIDS, 1993-2018



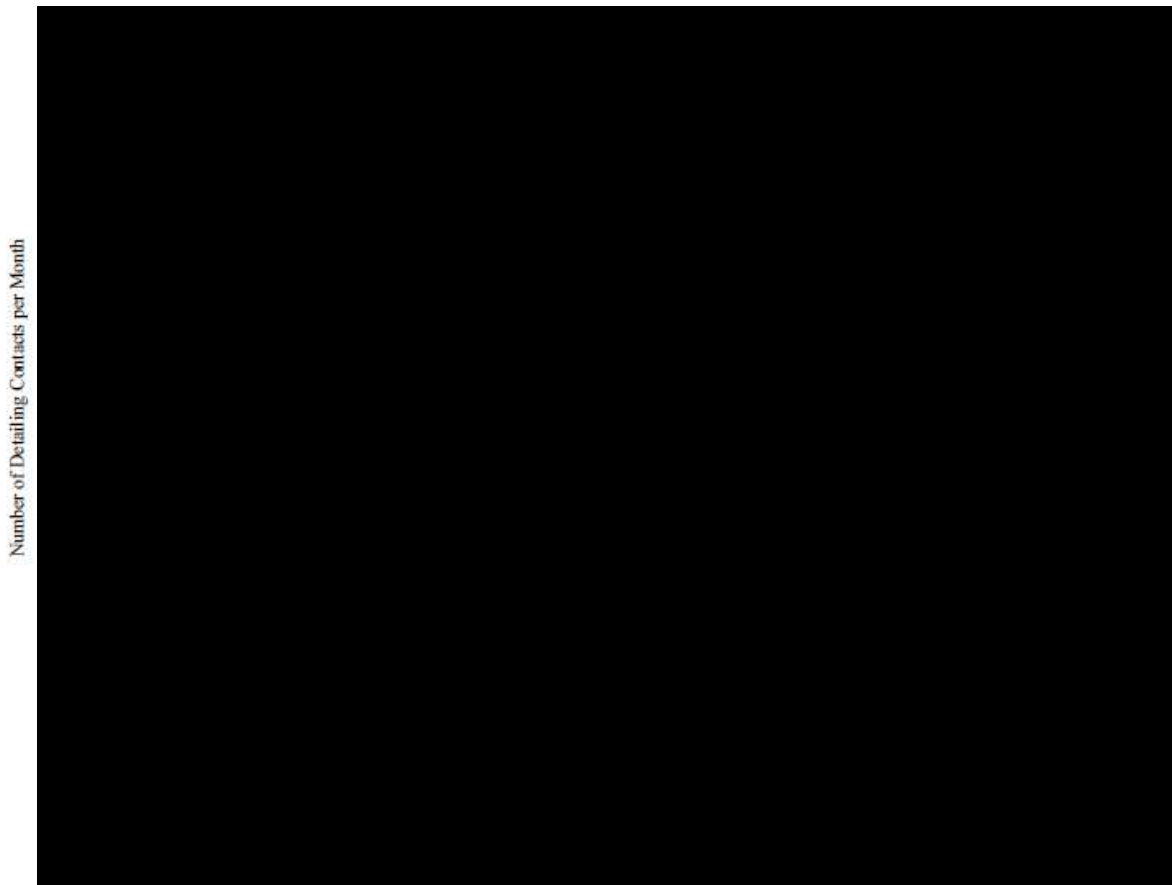
Source: IQVIA NPA, ARCOS, CDC.

55. Figure 4 shows the number of detailing contacts for the opioid drugs at issue from 1993 to May 2018 ([blue line](#), with scale on left axis). Detailing, which is undertaken by the brand-name drugs in the class, typically peaks during initial launch and ceases shortly before or after AB-rated (bioequivalent) generic drugs enter. As can be seen in the figure the number of detailing contacts per month ebbed and flowed during the 1993-2018 period. All Defendant brand-name drug manufacturers promoted their products through detailing during the period of the alleged misconduct. For each brand-name manufacturer Defendant Attachment C lists the products at issue, and shows their aggregate MMEs and detailing contacts. Figure 4 also

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shows estimates of the stock of promotion using alternative depreciation rates (scale on right axis). At a depreciation rate of 0%, the stock reflects the cumulative amount of detailing undertaken to date; by the end of the period, over [REDACTED] detailing visits had taken place.

FIGURE 4
DETAILING FOR ALL OPIOIDS



The Rationale for and Implications of Using Detailing as the Measure of Conduct

56. The manufacturer Defendants used a panoply of both branded and unbranded marketing tactics to increase opioid sales. While documents produced in discovery show many

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examples of such promotional efforts beyond detailing⁸⁸ that I understand Plaintiffs intend to prove were illegal, for the purposes of my econometric analysis, I rely on detailing contacts (i.e., the number of visits to physicians and other providers) to measure promotion for several reasons. First, for opioid products, detailing is by far the dominant form of promotion.⁸⁹ IQVIA reports no spending for professional journal advertisements and direct-to-consumer advertising for the opioid products relevant to this litigation. While there is some report of free samples, the number extremely low over the period, particularly after 2000. Second, pharmaceutical marketing programs typically combine various forms of marketing such that, were there to be an increase or decrease in promotional detailing, it is reasonable to expect that some other forms followed that course. From an econometric standpoint, detailing is a good proxy for total promotional effort. Third, alternative measures of promotion that I could obtain from available sources have substantial missing data (e.g., estimates of payments to pain advocacy groups can only be obtained from the records of some but not all manufacturers for a subset of years) and would restrict my ability to examine the impact of promotion on sales over the entire period of interest. Note that in this case, there appears to be substantial evidence that through means other than promotional spending the Defendant manufacturers fundamentally changed opioid prescribing standards. The direct approach does not calculate the effects of the non-promotional marketing, and is thus conservative. In short, I am confident in my direct-method

⁸⁸ For examples, see CHI_000169914 at 962 and 963; JAN-MS-00494171 at slides 12-52; MNK-T1_0000913808; TEV_FE00030796 at 802 and 804; EPI000300652 at slide 80; and ALLERGAN_MDL_00450170, as well as documents cited in footnotes 70-71 above.

⁸⁹ In his report, Dr. Perri also cites the importance of “personal selling” quoting an Endo document that states: “Sales force detailing is the most impactful tactic, detailing accounts for ~35-65% of all sales and marketing impact.” Perri Report, ¶ 59.

estimates not only because of the relative importance of detailing, but also because detailing is often used in concert with other forms of promotion including samples and yields conservative results.

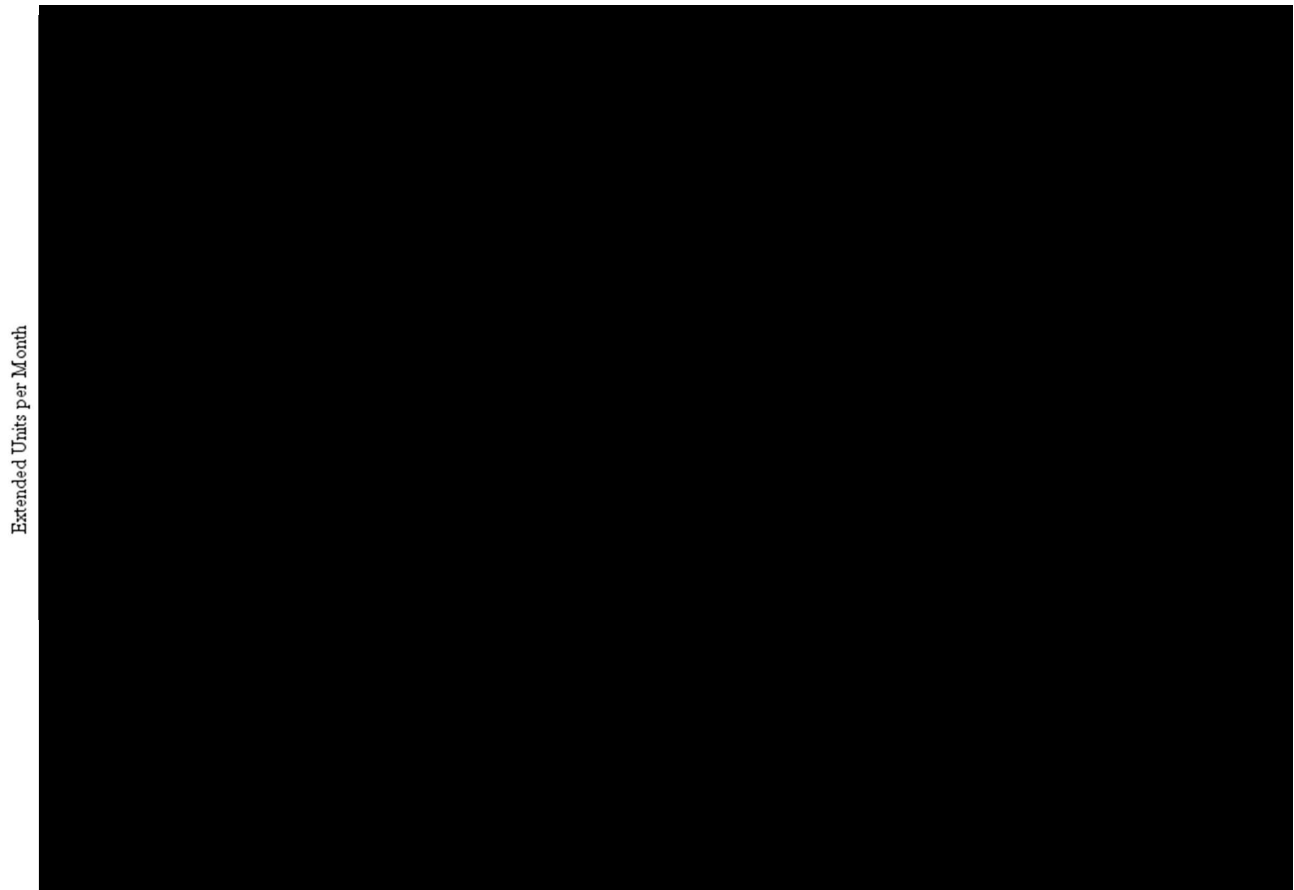
57. Figure 5 is a timeline of key events. According to Plaintiffs' experts and the published literature, the perceptions of physicians and the public evolved as a direct result of the alleged misconduct.⁹⁰ These changes – which were the result of the Defendants' actions -- would have affected the receptiveness of prescribers and patients to promotional messages about the safety and effectiveness of opioids. Figure 5 shows key events identified by Plaintiffs that helped promote expanded opioid prescribing (in green), and subsequent public health and regulatory events (in red) that signaled the growing realization about the dangers of opioid use.⁹¹

⁹⁰ "Defendants worked to create aggressive marketing strategies for opioids which served to distort needs, wants, and demand for opioids." Perri Report, ¶ 119.

⁹¹ The arc of the opioid epidemic has been chronicled elsewhere. For example, L. Machikanti, *et al.*, "Opioid Epidemic in the United States," *Pain Physician*, Vol. 15, 2012, es9-38. M. Jones, *et al.*, "A Brief History of the Opioid Epidemic and Strategies for Pain Medicine," *Pain Therapy*, Vol. 7, 2018, pp. 13-21. A. Alam and D. Juurlink, "The prescription opioid epidemic: An overview of anesthesiologists," *Canadian Journal of Anesthesiology*, Vol. 63, 2016, pp. 61-68. FDA, "Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse" (<https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm>). Expert Report of Theodore Parran, in this matter, March 25, 2019 (hereafter "Parran Report"), Sections IV.E-F and I-J. Expert Report of Mark Schumacher, in this matter, March 25, 2019 (hereafter "Schumacher Report"), Section III.B.3.

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FIGURE 5
TIMELINE OF KEY EVENTS



Source: IQVIA NPA, ARCOS, CDC.

B. Analytic Approach

58. To quantify the effect of promotion on total sales of opioids I use a standard econometric technique: multiple regression. Multiple regression techniques allow the analyst to separately quantify the influence of multiple economic variables on an outcome. Time-series regression, which is the particular technique I use in this case, examines patterns over time for a single unit of analysis (here, the United States retail pharmaceutical market) to capture a dynamic causal relationship. Because pharmaceutical sales in a particular period are related not

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only to pharmaceutical promotion in that period, but also to promotion that occurred in prior periods, a dynamic model is well-suited to the question at hand.

59. My primary dependent variable (the outcome to be explained) is the number of MMEs for all drugs at issue in this matter. This is the measure of impact that is conceptually connected to the harms that are quantified in the report by Prof. David Cutler. In Attachment D I show that a similar cause and effect relationship can be demonstrated for the number of extended units.

60. The key explanatory variable in the model is the number of detailing contacts for opioids. Consistent with the theory of demand I also include a class-wide price index⁹² for opioid drugs. Finally, in an expanded model, I include variables that capture some of the key events in the timeline described above.

61. The basic regression model can be expressed in the following form:

⁹² Given the long time period with entry and exit of opioid products, I construct a Fisher Ideal Price Index. More information on the price index is provided in Attachment D.

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$$Q_t = \alpha + S_t' \beta + X_t' \gamma + e_t \quad (1)$$

Where:

Q_t is the number of opioid MMEs sold at retail in month t

S_t is a vector measuring the stock of detailing contacts for all opioids at month t

X_t is a vector of factors other than detailing that change over time, including prices and variables that capture events such as the issuance of new clinical guidelines for the treatment of pain

e_t is an error term

α, β and γ are coefficients to be estimated

62. Detailing contacts were entered into the model as a stock, including the number of current contacts and the depreciated value of past contacts, in line with the published literature and in accordance with the theory that effects of promotion on prescribing are dynamic.⁹³ The stock of contacts in month t, S_t , was computed as follows:

$$S_t = \text{Contacts}_t + (1 - \delta) S_{t-1} \quad (2)$$

Where:

Contacts_t is the number of detailing contacts in month t, and

S_{t-1} is the depreciated value of past contacts.

The parameter δ is the depreciation rate, which I estimate in the model along with the other parameters.

⁹³ See discussion in ¶ 33 above.

63. In specifying the model, I include the right-hand side variables in levels without transformation. As discussed in more detail below, I allow the impact of the stock of promotion to change over time based on specification tests. A full description of the model and related statistical output appears in Attachment D.

64. The econometric analyses serve two purposes. First, they indicate that in economic terms there is a causal relationship between the Defendants' promotion and prescriptions of opioids so that if the allegations of misconduct are proven true, impact can be found. Second, I use the models to simulate what the level of prescribing would have been if the Defendants had not engaged in the alleged misconduct, as measured by their detailing contacts. That is, I alter the underlying values of the promotional stock to replicate a "but-for" world and predict but-for quantities.

C. Results

65. Starting from the basic model described in Equation 1 above, I sequentially build models to account for the different ways the opioid prescribing unfolded into an epidemic over time. Consistent with facts summarized in this matter and the observations I made based on the figures above, I hypothesized that the impact of detailing would change over time as beliefs and norms about opioid treatment change. To account for these changes, I empirically identify changes, or "breaks" in econometric terms, in the relationship between detailing and sales over time. Ultimately, the data reveal there were three eras in the life of opioid detailing: (1) the period before wide acceptance of expanded use of opioids for pain,⁹⁴ (2) rapid growth after

⁹⁴ See also Parran Report, ¶¶ 125-28.

alleged efforts to co-opt pain guidelines and other norm-setting activities, and (3) the period of cumulative impact of countervailing factors such as the introduction of mandatory prescription drug monitoring programs and new treatment guidelines. (For a more complete picture see the events marked in red in Figure 5).

66. While the Defendants actively sought to manipulate the scientific and popular understanding of the risks of opioids prior to 1999, according to the plaintiffs' marketing expert Perri,⁹⁵ the release of the American Pain Society and American Association of Pain Medicine (APS, AAPM) consensus statement on pain (Spring 1997)⁹⁶ followed by the Federation of State Medical Board (FSMB) model guidelines (May 1998)⁹⁷ and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) pain management standards (2001)⁹⁸ were also important marketing tools.⁹⁹ Through such advocacy as well as traditional marketing vehicles, Dr. Perri finds that Defendants sought to change the narrative about opioid therapy, opening the floodgates to prescribing.¹⁰⁰

⁹⁵ Perri Report, ¶¶ 72-74.

⁹⁶ American Academy of Pain Medicine and the American Pain Society, "The use of opioids for the treatment of chronic pain – A consensus statement from the American Academy of Pain Medicine and the American Pain Society," *Journal of Pain*, 6(1), 1997, pp. 77-79.

⁹⁷ Federation of State Medical Boards, "Model policy for the use of controlled substances for the treatment of pain," *Journal of Pain and Palliative Care Pharmacotherapy*, 19(2), 2005, pp. 73-78.

⁹⁸ D. Phillips, "JCAHO pain management standards are unveiled," *JAMA*, 284(4), 2000, pp. 428-29.

⁹⁹ "Reshaping the minds of prescribers through CPG [Clinical Practice Guideline] development and associated distribution of these guidelines through educational (marketing) activities was an important aspect of Defendants marketing because of the impact it could have on sales." ⁹⁹ Perri Report, ¶ 80.

¹⁰⁰ Specifically, Dr. Perri concludes: "Defendants' messages (discussed in detail below) focused on translating drug features into drug benefits, and downplayed information that would serve to discourage prescribing, including potential harms." Perri Report, ¶ 121). "In addition to downplaying addiction, Defendants' marketing also attacked mainstream thinking about dependence, claiming that patients can easily be tapered off opioids, and that dependence is not a significant concern." Perri Report, ¶ 137.

67. The accelerated growth in opioid prescribing that followed these guideline and messaging changes continued for approximately a decade before it was finally arrested and ultimately reversed by the cumulative effects of physician leadership, media attention, public health surveillance and regulation. During this period, as Dr. Perri notes, “While the pharmacology of opioids did not substantially change, the marketing of opioids did.”¹⁰¹ (Perri, ¶114)

68. Thus, in my preferred empirical specification, I model the effects of detailing on the number of MMEs sold at retail using a “piecewise” model, where the coefficient on the stock of detailing is estimated separately during each of the three eras. Not only does this approach correspond to observed changes in prescribing attitudes and guidelines for prescription opioids but also it tracks the patterns of the sales data presented in Figure 2. Models in which we assume the impact of promotion is constant over time do not fit the underlying data well. (I will return to this point below in comparing the fit of alternative regression models).

69. Table 1 shows the coefficient estimates and p-values for three alternative regression models that capture the relationship between detailing and sales. All models include an estimated constant term and a depreciation rate for the stock of promotion (the parameter δ). The effectiveness of detailing is reflected in the parameters β , β_1 , β_2 and β_3 .

¹⁰¹ See *e.g.*, U.S. Department of Justice, “Statement of United States Attorney John Brownlee on the Guilty Plea of the Purdue Frederick Company and Its Executives for Illegally Misbranding OxyContin,” May 10, 2007 (https://archive.org/stream/279028-purdue-guilty-plea/279028-purdue-guilty-plea_djvu.txt); U.S. Department of Justice, U.S. Department of Justice, “Pharmaceutical Company Cephalon to Pay \$425 Million for Off-Label Drug Marketing,” September 29, 2008 (https://www.justice.gov/sites/default/files/civil/legacy/2014/01/09/Cephalon_Press_Release.pdf).

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Table 1
Regression Estimates: Impact of Detailing on Sales in MMEs, 1993-2018

Parameters		Model A		Model B		Model C	
Param.	Label	Estimate	Sig.	Estimate	Sig.	Estimate	Sig.
α	Constant						
β	Stock of Promotion						
β_1	Stock of Promotion*Regime Dummy until Mar2002						
β_2	Stock of Promotion*Dummy from Mar2002						
β_3	Stock of Promotion*Dummy Trend from Aug2010						
δ	Depreciation Rate Constant						
γ_1	Consensus Statement From AAPM/APS 01/1998						
γ_2	Federation of State Medical Boards Guidelines 01/1999						
γ_3	JCAHO pain standards released 01/2001(*)						
γ_4	OxyContin Reformulation 08/2010						
γ_5	Hydrocodone Rescheduling 10/2014						
γ_6	Aggregate Price Index						
RSquare							
AdjRSq							

70. Model A assumes that the effectiveness of detailing is constant over the period 1993-2018; the regression coefficient measuring effectiveness (the parameter β) and is estimated to be [REDACTED] MME/month for a unit change in the stock of promotion. The estimated constant term is [REDACTED] MME and the monthly depreciation rate is not statistically different from zero. The price index, with a coefficient of [REDACTED], is statistically significant and in the expected direction (higher prices lead to lower MMEs). For Model A, the R-squared statistic [REDACTED], which shows how well the estimated relationship fits the underlying data, is notably lower than for the other models, reflecting the fact that a constant relationship between the

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stock of detailing and sales leaves much variation in sales unexplained. The predicted values for Model A are shown in Figure 1A in Attachment D. Model A does not capture well either the initial growth in opioid sales or the change that occurred in 2011. In short, estimating Model A teaches us that there is likely a changing, not constant, relationship between detailing and sales over this long (1993-2018) time period that should be explored to more accurately describe the relationship.

71. Model B allows the effectiveness of promotion to change at two points in time, determined using specification tests. Thus, this model captures three different periods or eras of the opioid market: the initial era, an increase in MME sales during the second era, and a third era marking the gradual decline in MME sales. Specifically, we allow for an additive shift in promotional effectiveness that occurs in April 2002 (which enters as the interaction between the stock of detailing and a dummy variable that is zero before and 1 after April 2002) and then with a secular decrease in promotional effectiveness that begins in September 2010 (which enters as the interaction between the stock of detailing and a linear trend that is zero before September 2010 and increments by month).¹⁰² The predicted values for Model B are shown in Figure 1B in Attachment D.

72. The effect of the stock of detailing promotion in Model B is estimated to be 934 MME/month for a unit of promotion stock between 1993 and April 2002. At that point, the effectiveness of promotion increases to [REDACTED] MME/month, a nearly [REDACTED] increase in the effectiveness of promotion. Beginning in September 2010 the effectiveness of promotion sales

¹⁰² See Attachment D.

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begins to drop by █ MME per month. Model C results in an estimate for the constant term of █ billion MME. The depreciation rate of █ translates to an annual rate of █. A negative depreciation rate indicates that the stock of promotion grows over time. While this prediction may be at odds with the usual marketing literature, it is perfectly consistent with an addictive product like opioids.¹⁰³ The coefficient on the price index is █, which again is statistically significant. The predictive power of Model B is shown to be quite good with an R-square of █, thus explaining over █ of the variation in MME sales.

73. While shifts in the effectiveness of promotion in Model B implicitly accounts for non-detailing events and policies, I tested the robustness of Model B by examining whether indicators of specific events and policies should be *explicitly* included in my model. To test for the impact of specific events on the empirical model, I introduced dummy variables for several of the events shown in Figure 5 and discussed in ¶¶ 57 and 65. These dummy variables are set to zero up to the month in which the event occurs and one thereafter. The three-era model with five event dummies is shown as Model C in Table 1. Model C uses the same turning points as used in Model B (i.e., April 2002 and September 2010). Three of the five dummy variables are insignificant, the two other dummies are significant at the █ level of significance. The first is the 1999 Federation of State Medical Boards Model Guidelines which suggests an increase of █ MME/month. The second event for which a significant effect was detected is the rescheduling of hydrocodone which counterintuitively suggests an increase of █

¹⁰³ “Additionally, because prescription opioids may result in tolerance, dependence, and/or addiction, the overall “demand” for opioids is distorted by pharmaceutical marketing aimed at increasing the use of these drugs. I refer to this as a distortion because, whether due to tolerance, dependence, or addiction, some patients who use opioids require and/or seek more opioids over time.” Perri Report, ¶ 32.

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MME per month. Jointly, all five events are not statistically different from zero. It is also worth noting that the adjusted R-squared statistic (which adjusts for the number of additional variables included in the model) in Model C barely improves upon the adjusted R-squared in Model B and the main results concerning promotion and price are little changed. While I could add more events to the model, on its face this approach seems inconsistent with the underlying data, which rise and fall relatively smoothly (ignoring monthly fluctuations around the trend).

74. Given these results and applying accepted principles of econometrics, I am of the opinion that Model B is a fair, accurate and econometrically sound method by which to estimate the relationship of the Defendants' detailing of opioids on the sales of prescription opioids over the time period 1993 to 2018.

Calculation of But-For MMEs

75. I have been instructed by counsel to assume in my but-for scenarios that the fact finder (judge or jury) finds that all or virtually all promotion by the manufacturer Defendants from 1995 to the present was unlawful. (I later show that the model I present can be adjusted to reflect other assumptions about the fact finder's conclusions). Thus, to calculate impact for the purpose of damages beginning in 2006, I model a world in which this promotion did not occur (i.e, but-for promotion equals actual promotion for opioids less all promotion for opioids by the Defendants and their surrogates). To calculate the number of MMEs that would have been filled but-for the alleged wrongdoing, I replace actual detailing with but-for detailing and generate monthly predicted but-for MMEs. Attachment D provides details of the methods, assumptions and inputs for the but-for scenario. I then take the differences between predicted

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actual MMEs and the predicted MMEs that would have been prescribed and purchased under the assumption of the but-for scenario. These results are presented in Table 2.

TABLE 2
DIRECT MODEL B: ANNUAL ESTIMATES OF IMPACT OF MANUFACTURER MISCONDUCT
1995-2018

YEAR	PERCENT OF MMEs ATTRIBUTABLE TO CHALLENGED [REDACTED]
[REDACTED]	[REDACTED]
1996	[REDACTED]
1997	[REDACTED]
1998	[REDACTED]
1999	[REDACTED]
2000	[REDACTED]
2001	[REDACTED]
2002	[REDACTED]
2003	[REDACTED]
2004	[REDACTED]
2005	[REDACTED]
2006	[REDACTED]
2007	[REDACTED]
2008	[REDACTED]
2009	[REDACTED]
2010	[REDACTED]
2011	[REDACTED]
2012	[REDACTED]
2013	[REDACTED]
2014	[REDACTED]
2015	[REDACTED]
2016	[REDACTED]
2017	[REDACTED]
2018	[REDACTED]
TOTAL	[REDACTED]

Sources: IQVIA NPA, IPS, ARCOS, CDC. 2018 based on data from January – May only
But-For calculations described in Attachment D.

Estimates are based on Model B in Table 1.

The percent of MMEs attributable to challenged promotion is calculated as the difference between predicted actual and predicted but-for MMEs assuming all Defendants' promotion is set to zero starting in 1995, divided by predicted actual MMEs.

Sensitivity with Respect to Specific Defendants

76. As noted in my assignment, I have examined the sensitivity of my calculations of impact to the inclusion or exclusion of particular Defendants' promotional efforts in the construction of my but-for scenario. In the first row of Table 3, I show the impact of manufacturer misconduct on MMEs from 1995-2018 with a but-for scenario that assumes none of the Defendants' marketing was lawful. In each of the subsequent rows, Table 3 shows the impact of manufacturer misconduct on MMEs from 1995-2018 while assuming the promotion by one Defendant at a time is deemed lawful (and therefore is allowed to generate prescriptions in the but-for scenario).

Table 3
Aggregate Percent Harm Excluding Individual Defendants From Litigation
1995-2018

Defendants Excluded From Litigation	Aggregate Harm Including Selected Defendant in But-For
Baseline (No defendants excluded)	
Actavis	
Dupont	
Endo Labs	
Insys Therapeutics	
Janssen	
Mallinckrodt	
Purdue	
Teva	
Non-Defendant (promoting Defendant drugs)	

77. My detailed backup materials, described in Attachment D, demonstrate that I can produce impact estimates for any combination of Defendants and years for which the plaintiffs can prove unlawful conduct. In addition, my backup includes illustrative impact estimates

assuming (a) a given percentage of Defendants' promotion is assumed to be lawful, (b) promotion for a given specialty group is assumed to be lawful (e.g., oncologists), and (c) promotion for a given drug is assumed to be lawful.

IX. ECONOMETRIC ANALYSIS – INDIRECT APPROACH

78. As noted earlier, the direct method of estimation is limited in part by the extent to which we can measure and include in the models all of the tactics allegedly employed by the Defendants, including manipulation of various professional societies and accrediting bodies. An alternative method of identifying the impact of the Defendants' misconduct is to use an indirect method.

79. The indirect method begins with a regression analysis of the relationship between opioid sales and the demographic, economic, and health care characteristics of an area, ideally during the period prior to the misconduct. Because these factors change very slowly and often move in concert over time, the indirect approach requires a different type of data and approach than the direct method. In particular, we employ data at the county level where there is substantial geographic variation in demographic, economic, and health care characteristics and run the regression for a single cross-section in the "pre-misconduct" period (in fact, the earliest data we have is 1997 our results are likely conservative). This regression is then used to predict sales that would have been expected given only changes in economic, demographic, and health care factors. Similar to the but-for calculations of sales using the direct method, predictions from the indirect method represent an estimate of opioid sales in the absence of Defendants' misconduct.

80. The regression equation used in the indirect approach here can be written simply as:

$$\text{Opioid Sales}_i^{\text{Pre}} = X_i^{\text{Pre}} \beta + \varepsilon_i$$

The regression captures the relationship between sales at a point in time in county i and a set of economic, demographic, and health care characteristics of the county (X_i). The coefficients in the regression (β) capture the relationships between the explanatory variables and sales, while ε_i reflects the portion of the county-level sales that is not explained by the regression.

81. Based on these estimates of the relationship between the economic, demographic and health care characteristics of counties and opioid sales before the opioid epidemic took hold, the model can be used to predict opioid sales using only changes in the X_i variables over time. A modified version of this approach incorporates an estimated secular trend, also using data from the pre-misconduct period. Incorporation of the secular trend into the model is conservative in that it assumes that none of the X_i variables contributed to that trend. In our context, adding the trend to the predictions is a way of capturing the market expanding effects of non-Defendant promotion.

82. The indirect model is a form of “residual” analysis that is widely used to evaluate economic impact. Residual analysis is useful when the variable of interest cannot be measured with precision – in this case, that variable is the full set of tactics used by the Defendants to

increase opioid use. My approach follows an established methodology that has been widely used in health economics,^{104,105,106} macroeconomics,^{107,108} and labor economics.¹⁰⁹

A. Data and Methods

83. The indirect model uses county-level ARCOS data on shipments (sales) of prescription opioids between 1997 (the first year for which data are available) and 2016 (the last year for which we have the ARCOS data). For the purposes of the analysis, the measure of sales in MMEs is expressed in per capita (per day) terms to account for the variation in population across counties.¹¹⁰ There are some small differences between the ARCOS data and the IQVIA data used in my direct analysis. With the IQVIA data, precise delineations can be made between Schedule II and Schedule III opioids, which allow me to exclude drugs that are always Schedule III from the analysis. With the ARCOS data, this refinement is not possible. This problem is *de minimus*, however, affecting less than 2.5 percent of the drug shipments in ARCOS.

¹⁰⁴ D. Cutler, *et al.*, "Are Medical Prices Declining? Evidence from Heart Attack Treatments," *Quarterly Journal of Economics*, 113(4), 1998, pp. 991-1024.

¹⁰⁵ D. Cutler and E. Meara, "The Technology of Birth: Is It Worth It?" in Alan Garber, ed., *Frontiers in Health Policy Research, Volume 3*, Cambridge, MA: MIT Press, 2000, pp. 33-67.

¹⁰⁶ J. Newhouse, "Medical Care Costs: How Much Welfare Loss?" *Journal of Economic Perspectives*, 6, 1992, pp. 13-29.

¹⁰⁷ R. Solow, "Technical Change and the Aggregate Production Function," *Review of Economics and Statistics*, 39, 1957, pp. 312-20.

¹⁰⁸ A.C. MacKinlay, "Event Studies in Economics and Finance," *Journal of Economic Literature*, XXXV, 1997, pp. 13-39.

¹⁰⁹ S. Firpo, T. Lemieux, and N. Fortin, "Decomposition Methods in Economics", in D. Card and O. Ashenfelter, eds., *Handbook of Labor Economics*, 4th Edition, North Holland: Elsevier, 2011, pp. 1-102.

¹¹⁰ See Attachment D.

84. I include three sets of explanatory variables in the indirect model. Demographic variables in the model include the percent of the population that is male, the percent in different age groups (<15, 15-29, 30-44, 45-64, 65+), the percent of the population that is white, the percent that is black, the percent that is Hispanic, the share of the population in four different education groups (less than a high school degree, a high school degree, some college, and a college degree), and the percent of the county identified as urban.¹¹¹ Economic variables are also included to capture the idea that the same economic conditions that have been shown to be causally related to opioid deaths may also increase the demand for opioids. In particular, I include the unemployment rate and employment-to-population ratio; the distribution of employment by major industry sector; median household income (\$000); the poverty rate; and the county's population.¹¹² Finally, I include two variables to capture the specific health care factors that may reflect demand for opioids: the percentage of the population without insurance coverage; and the number of cancer deaths.¹¹³

85. I use a log-linear specification for ease of interpretation. In particular, the coefficients on the socioeconomic indicators (those expressed as rates) can be read as increasing or reducing sales by a certain percentage. The model is estimated using ordinary least squares.

¹¹¹ The variables used in the regression analysis, including means, are reported in Attachment D.

¹¹² The explanatory variables in the indirect model parallel those used in research literature in this field. A. Case and A. Deaton, "Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century," *Proceedings of the National Academy of Sciences*, 112(49), 2015, pp. 15078-83. A. Case and A. Deaton, "Mortality and morbidity in the 21st century," *Brookings Papers on Economic Activity*, 2017, pp. 397-476. C. Ruhm, "Deaths of despair or drug problems?" National Bureau of Economic Research Working Paper No. w24188, 2018.

¹¹³ Data sources are described in Attachment D.

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B. Results

86. **Table 4** reports the results for the indirect regression. The overall model fits well (note that R-squared statistics for cross-sectional models are lower than time series models), with an adjusted R-squared statistic of 0.33. Counties with younger populations, lower household incomes, higher percentages of people having some college education, lower percentages of Black and Hispanic people, more urban populations, and more cancer deaths have higher sales.

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TABLE 4
OLS REGRESSION RESULTS
INDIRECT METHOD

Variable	
Log of Shipments per Capita	
Percent Male	
Percent Under 15	
Percent 15 to 29	
Percent 30 to 44	
Percent 45 to 64	
Percent White	
Percent Black	
Percent Hispanic	
Percent Less High School	
Percent High School	
Percent Some College	
Employment Ratio	
Percent Unemployed	
Median Household Income (Thousands)	
Percent Ag/M/Const/Util	
Percent Manufacturing	
Percent Retail/Transportation	
Percent Professional	
Poverty Rate	
Percent Urban	
Census Population (Thousands)	
Cancer Deaths Per 1,000	
Percent Uninsured	
Constant	
Standard errors are estimated robustly.	

Notes: Primary data source is ARCOS Large County sales data. All sources and detailed methods included in Attachment D.

87. The results of the regression model, together with data on explanatory variables for 1998-2016 are used to predict MMEs for the post-1997 period that would have been observed in the absence of Defendants' alleged misconduct. To the account for secular trends that are

not captured by demographic, economic and health care variables in the model I also add to the predicted MMEs an annual increase based on an estimated linear trend using historical data that pre-date the alleged misconduct. For this trend estimate, I rely on data from the International Narcotics Control Board, which are available nationally back to 1980.¹¹⁴ I chose a fifteen year trend (1980-1995) to minimize the influence of any year-to-year variations in annual sales and to capture underlying changes in clinical practice and other unmeasured influences.¹¹⁵ Given that some part of this secular trend derived from national sales data is likely driven by the same variables I include in my analysis, inclusion of this additional trend renders my analysis conservative.

88. I also adjust for the impact of aggregate prices for opioids. There is little county-level variation in opioid prices so this variable does not appear in the cross-sectional model, despite the fact that my direct model shows a small but significant (negative) effect of price on sales over time. To account for these price increases I adjusted the but-for MMEs as follows. The estimated coefficient on the drug price index from the direct-model regression was adjusted to reflect the average difference in annual MMEs between the IQVIA and ARCOS data. This adjusted coefficient was multiplied by the increase in the price index for each year and the product was added to but-for annual MMEs estimated from the county-specific demographic, economic and health-policy variables. As the predicted effect of rising prices on but-for MMEs

¹¹⁴ International Narcotics Control Board (INCB), United Nations (UN). Data are available for the U.S. as whole and are comparable for national estimates of MME per capita from ARCOS.

¹¹⁵ Inclusion of any trend here is conservative. My specific choice of trend is conservative relative to Dr. Parran's opinion that "Therefore, the baseline for opioid prescribing in American medical practice should be considered to be in the late 1970s through the late 1980s, rather than any time afterwards." Parran Report, ¶ 128.

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is negative, this adjustment reduces the but-for value and increases the estimated excess MMEs. But the relatively low elasticity of demand means the adjustment is small, reducing the excess share of total MMEs from the indirect model by an average of [REDACTED] percentage points per year.

89. Actual opioid sales increased sharply after 1995 but projections from the indirect regression model indicate that opioid sales would have grown much more slowly in the absence of Defendants' actions. Table 5 below reports the annual estimates of percentage impact for manufacturer misconduct based on the indirect method (analogous to Table 2 for the direct method).

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TABLE 5
INDIRECT METHOD: EXCESS SHIPMENTS IN MMEs

		Adjusted for Aggregate Opioid Prices	
Year	Total MME (MM)	Excess MME Adj (MM)	Excess Share Adj
1995			
1996			
1997			
1998			
1999			
2000			
2001			
2002			
2003			
2004			
2005			
2006			
2007			
2008			
2009			
2010			
2011			
2012			
2013			
2014			
2015			
2016			
Total			

Sources: U.S. Census data; INCB; and ARCOs. Details of this calculation are presented in

[REDACTED]

X. DOES A THEORY OF “UNDER-TREATED PAIN” EXPLAIN THE GROWTH IN OPIATE PRESCRIBING?

90. As an alternative to the Defendants’ marketing as being the explanation for much of the rise of opioid prescribing in the United States, I understand that some have argued an alternative explanation – that pain was previously “under-treated,” and that the growth in opioid shipments is due to either to the amount of pain in the United States increasing over time or, more likely, to the amount of the opioids used to properly treat pain increasing over this time period. For example (and while the plaintiffs allege that the Defendants improperly manipulated this movement) some groups encouraged increased use of opioids for treatment for pain management, referring to pain as “the fifth vital sign.”¹¹⁶

91. To test this hypothesis, I note there is empirical research on the prevalence of uncontrolled pain among cancer patients and other patient groups that could help us understand how much of the growth in opioid shipments could, as a theoretical matter, even possibly be attributed to using more opioids to treat pain consistent with medical evidence.¹¹⁷ In this section, I use epidemiologic data and a simple simulation approach to approximate the portion of the increased prescribing caused by the allegedly unlawful promotion could possibly be associated with using opioids to address ostensibly “under-treated” pain.¹¹⁸

¹¹⁶ M. Max, *et al.*, “Quality improvement guidelines for the treatment of acute pain and cancer pain,” *JAMA*, 274(23), 1995, pp. 1874-80.

¹¹⁷ R. Portenoy and Thaler, *et al.* “Pain in ambulatory patients with lung or colon cancer,” *Cancer*, 70(6), pp. 1616-24. C. Cleeland, *et al.*, “Pain and Its Treatment in Outpatients with Metastatic Cancer,” *New England Journal of Medicine*, 330(9), 1994, pp. 592-96. J. M. Donovan, *et al.*, “Incidence and characteristics of pain in a sample of medical-surgical inpatients,” *Pain*, 30(1), 1987, pp. 69-78. R. Marks and E. Sachar, “Undertreatment of Medical Inpatients with Narcotic Analgesics,” *Annals of Internal Medicine*, 78(2), 1973, p. 173-81. K. Sriwatanakul, “Analysis of Narcotic Analgesic Usage in the Treatment of Postoperative Pain,” *JAMA*, 250(7), 1983, 926-29.

¹¹⁸ I would note that Dr. Parran rules out clinical need as a reason for the increase in opioid prescribing, stating in his report that “There was no clinical reason for this avalanche of pills” (¶ 135).

92. Specifically, I conduct a thought experiment that allows me to calculate an “upper bound” of how much of the growth in MMEs could be attributable to more intensive pain management for patient groups that according to plaintiffs’ experts could have benefitted from treatment with opioids. All of the underlying assumptions in this section have been developed in reference to the opinions of the plaintiffs’ clinical experts, including Dr. Schumacher and Dr. Parran.¹¹⁹ As a general matter and for purposes of this empirical test, I assume: (i) that, at most, opioids are properly indicated for the short-term treatment of severe acute pain (e.g. trauma or post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease; (ii) that chronic opioid therapy is not recommended for most common chronic pain conditions (defined as moderate to severe pain lasting beyond 60 to 90 days), including low back pain, centralized pain such as fibromyalgia, and headache pain; and (iii) that in less common chronic pain conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated) for moderate and severe pain.

93. Plaintiffs’ experts point to the literature and clinical guidelines as benchmarks for appropriate opioid treatment.¹²⁰ While the experts acknowledge that there will be variation in dosing and duration in real world practice, I understand that the guideline-centered assumptions I make in my thought experiment represent a reasonable expectation of the modal

¹¹⁹ See the Parran Report, ¶¶ 45-47, 110, 145, and 190, and Schumacher Report, ¶¶ 119-26 and 132-35.

¹²⁰ See for example, Parran Report, Section IV.B-IV.E.

treatment – many patients would appropriately be treatment with lower doses and durations, while some would require more. Given the narrow categories of indicated chronic pain use, its role as third-line therapy, and the significant risks associated with its use, optimal chronic opioid therapy is difficult to characterize even in this approximate way with a single regimen. For these reasons, I do not attempt to capture optimal treatment for patients with chronic pain in my simulation.

94. My simulation of a theoretical maximum, scientifically-accepted use of opioids begins with incidence data on the populations of interest and applies baseline and “upper bound” values for key parameters that factor into the number of MMEs that would hypothetically be consumed by these patient groups. The parameters needed to calculate potential scientifically-accepted uses are: (1) the number of patients treated, (2) the daily dose in MMEs, and (3) the duration of treatment in days. Total MMEs consumed for appropriate treatment would simply be the product of these parameters. Through this approach, I estimate the number of MMEs that could have been accounted for by theoretical maximum, scientifically-accepted use of opioids. I also conduct a simple sensitivity test that considers how large the quantum of appropriate uses could be if any one of my parameters is underestimated. Note that because I am not documenting the diagnoses and dosing associated with *actual* uses of opioids, I am not able to calculate how much of the increased use of opioids during the period in which the alleged misconduct occurred was *in fact* for clinically appropriate indications, dosages, and durations. Instead I make medical evidence-based calculations to examine the possibility that the rapid growth of opioid use could be explained by efforts to appropriately address an ostensibly unmet clinical need (i.e., so-called “under-treated” pain).

A. Cancer Patients at the End of Life

95. The first group of patients with potentially undertreated pain includes cancer patients at the end of life/in hospice. I use epidemiologic data on cancer deaths in each year to identify the size of this population.¹²¹ Studies published in the 1980s and 1990s found that 50-70% of cancer patients reported uncontrolled pain¹²² suggesting that perhaps there was room for increased treatment with opioids.

96. For my simulation I take a conservative approach and assume that 100% of cancer patients at the end of life need (and want) a high dose of extended release oral opioids. This assumption is extremely conservative in light of plaintiffs' clinical expert Dr. Parran's opinion that "Even in the context of acute, cancer or end-of-life pain, opioids are not a first option if the pain is mild and can be controlled with non-opioid analgesics."¹²³ For dosing, my baseline assumption is 80 MMEs per day, which is consistent with average dosing in cancer patients reported in published studies.¹²⁴ For the duration of treatment for cancer patients at the end of life, I use the average duration of treatment reported for cancer palliative care as my baseline: roughly 64 days, which is just below the average number of days patients spend in hospice

¹²¹ I understand that clinical experts opine that certain other cancer patients (those with breakthrough cancer pain, not at the end of life) and patients dying from other conditions may be appropriately treated with opioids. I do not separately attempt to identify these patients for lack of complete data and because I understand there is more clinical nuance to the use of opioids for these patients (see, for example Parran Report ¶141). Such need will likely, however, be captured in the range of my sensitivity analysis (where I model the results of a 50% increase in any of my parameters, including the target population).

¹²² Portenoy, *et al.*, *op. cit.* Cleeland, *et al.*, *op. cit.* J. Morris, *et al.*, "The effect of treatment setting and patient characteristics on pain in terminal cancer patients: A report from the National Hospice Study," *Journal of Chronic Diseases*, 39(1), 1986, pp. 27-35. H. Greenwald, J. Bonica, and M. Bergner, "The prevalence of pain in four cancers," *Cancer*, 60(10), 1987, pp. 2563-69.

¹²³ Parran Report, ¶ 145 and Schumacher Report, ¶ 133.

¹²⁴ A. Haider, *et al.*, "Opioid Prescription Trends Among Patients with Cancer Referred to Outpatient Palliative Care Over a 6-Year Period," *Journal of Oncology Practice*, 13(12), 2017, pp. e972-e981.

(about 70).¹²⁵ Finally, I calculate the MMEs that would be required to treat end-of-life cancer patients by multiplying the number of cancer deaths in each year by the daily dose in MMEs and duration of treatment in days.

B. Patients with Acute Pain

97. The second group of patients with potentially “under-treated” pain is the population that suffers from acute pain. According to WebMD, “Acute pain typically comes on suddenly and has a limited duration. It's frequently caused by damage to tissue such as bone, muscle, or organs, and the onset is often accompanied by anxiety or emotional distress.” I estimate the incidence of acute pain by capturing two key groups of patients that experience pain due to a time-limited medical event (as opposed to a chronic condition): patients who are treated for trauma and patients who undergo surgery.

Trauma Patients

98. I measure the incidence of trauma using statistics on emergency department visits where the reason for the visit was trauma. According to research published in 1999 only 15% of individuals who were seen in an emergency department for pain received an opioid, despite rating their pain as severe.¹²⁶ Thus, as with cancer, there may have been reason to increase the use of opioids to better manage pain for trauma and other acute pain in the emergency

¹²⁵ C. Carlson, “Effectiveness of the World Health Organization Cancer Pain Relief Guidelines: An Integrative Review,” *Journal of Pain Research*, 9, 2016, pp. 515-34, p. 521. M. Wachterman, *et al.*, “Association of Hospice Agency Profit Status With Patient Diagnosis, Location of Care, and Length of Stay,” *JAMA*, 305(5), 2011, pp. 472-79. Average time spent in hospice comes from this article: American Medical News, “Average Hospice Length of Stay is Falling,” February 2, 2012 (<https://amednews.com/article/20120201/profession/302019996/8/>), reporting research from the National Hospice and Palliative Care Organization.

¹²⁶ P. Tanabe and M. Buschmann, “A prospective study of ED pain management practices and the patient’s perspective,” *Journal of Emergency Nursing*, 25(3), 1999, pp. 171-77.

department. As I did for terminal cancer patients, I conduct a thought experiment in which I quantify the MMEs of opioids required to treat 100% of patients who experience trauma. Published guidelines, which Plaintiffs' clinical experts regard as an appropriate benchmark, recommend a daily regimen of 30 milligrams of an immediate release opiate such as hydrocodone¹²⁷ to control post-trauma pain for three to seven days.¹²⁸ Hydrocodone has an MME conversion factor of one, meaning that 30 milligrams delivers 30 MMEs. I use the seven day regimen¹²⁹ in my simulation and calculate the number of MMEs that would be required to treat acute trauma patients with opioid therapy as the product of the number of trauma patients multiplied by 210 (30 MMEs times 7 days).

Surgical Patients

99. Finally, I consider the treatment of patients who underwent surgery on either an inpatient or outpatient basis. According to studies published around the time the alleged misconduct began, 41% of post-surgical inpatients experienced moderate to severe pain.¹³⁰ Again, I assume conservatively in my thought experiment that 100% of patients receiving inpatient or outpatient surgical procedures would receive an opioid prescription. As in the case

¹²⁷ American Academy of Emergency Medicine, "White Paper on Acute Pain Management in the Emergency Department," approved October 24, 2017 (<https://www.aaem.org/resources/statements/position/white-paper-on-acute-pain-management-in-the-emergency-department>).

¹²⁸ From CDC guidelines for opioid prescribing, "When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed." D. Dowell, T. Haegerich, and R. Chou. "CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016," *Morbidity and Mortality Weekly Report*, 65(No. RR-1), 2016, p. 24 (hereafter "2016 CDC Guidelines").

¹²⁹ Note that this assumption is conservative relative to Dr. Parran's assessment: "For acute pain conditions, including post-surgery, opioid therapy should be used for only a very short period of time, not to exceed one or two weeks; in many instances of acute pain, two to five days of opioids is sufficient." Parran Report, ¶ 47.

¹³⁰ Marks and Sachar, *op. cit.* Sriwatanakul, *op. cit.*

of trauma patients, published guidelines advise a daily regimen of 30 mg of an immediate release opioid such as hydrocodone¹³¹ to control post-surgical pain for three to seven days.¹³² I use the seven day regimen in my simulation and calculate the number of MMEs that would be required to treat acute trauma patients with opioid therapy as the product of the number of surgical patients multiplied by 210 (30 MMEs times 7 days).¹³³

C. Results for Cancer and Acute Pain

100. Table 6 presents the results of the calculations I describe above for each patient group and in total, alongside actual MMEs sold. Figure 6 shows actual MME sales plotted alongside total hypothetical MMEs using the baseline assumptions for patients in the three groups to receive opioid therapy starting in 1995. The data show that changes in appropriate treatment for these groups of patients cannot explain the growth of opioid use during the period of alleged misconduct. The observed percentage increase in MME opioid sales between 1995 and 2011 (the peak of opioid MMEs) is [REDACTED].¹³⁴ The total uses that could be explained by cancer, surgery, and trauma based on clinically reasonable treatment regimens is less than [REDACTED] of total MMEs at the peak level of opioid prescribing in 2011. The empirical explanation for these

¹³¹ MD Anderson Cancer Center, University of Texas, "Post-Operative Pain Management," approved October 30, 2018 (<https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clinical-management-post-op-pain-web-algorithm.pdf>).

¹³² 2016 CDC Guideline, *op. cit.* Schumacher Report, ¶ 120.

¹³³ Once again, my assumption that all surgical patients might be appropriately given opioids goes beyond what plaintiffs' clinical experts have opined. Notably, Dr. Schumacher suggests limiting opioids for surgery patients. "It is better to avoid opioids if there are effective alternatives. Use the lowest possible dose for the least amount of time during recovery It is important to limit prescribing to what is actually needed, to avoid inappropriate usage, or more drug in people's medicine cabinets. After most routine surgery 3-7 days is often enough." Schumacher Report, ¶ 119.

¹³⁴ (Total MMEs Prescribed in 2011 – Total MMEs Prescribed in 1995) / Total MMEs Prescribed in 1995 x 100. See Table 6.

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findings is straightforward. First, the prevalence of these conditions is falling not rising over this time period, with an estimated [REDACTED] decrease between 1995 and 2011.¹³⁵ Second, even assuming that all of these cancer, surgery, and trauma patients were newly treated with the recommended dose and duration, the quantum of need is far exceeded by the flood of oral opioids that were sold by 2011.

101. The table also shows the sensitivity of my conclusions to proportional increases in any of the inputs. If any input were increased by 50% (or smaller increases in several inputs that yielded an overall increase of 50% in terms of the need for MMEs), appropriate use would still only account for only [REDACTED] of total opioid sales in MMEs over the period 1995 to 2018.

¹³⁵ Based on information from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP), Centers for Disease Control and Prevention (CDC) Surveillance, Epidemiology, and End Results (SEER), Health Resources and Services Administration (HRSA) Area Health Resource File (AHRF). See Attachments C and D.

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TABLE 6
MAXIMUM PERCENT OF MMEs EXPLAINED BY CLINICALLY JUSTIFIABLE USES

Year	National Estimates, 1993-2018					Actual MMEs Sold	Percent in Excess of Maximum Clinically Justifiable Opioid Uses
	Cancer	Trauma	Surgery	Total	Total + 50%		
1995							
1996							
1997							
1998							
1999							
2000							
2001							
2002							
2003							
2004							
2005							
2006							
2007							
2008							
2009							
2010							
2011							
2012							
2013							
2014							
2015							
2016							
2017							
2018							
Total							

Source: Epidemiological Data: AHRQ HCUP, CDC SEER, HRSA AHRF
Sales Data: IQVIA NPA, ARCOS, CDC

Notes: Total = sum of MMEs needed to appropriately treat 100% of cancer, trauma, and surgery given clinical parameters (Cancer: 80 MMEs/day over 64 days; Surgery and Trauma: 30 MMEs/day over 7 days). Actual MMEs nationally from IQVIA NPA, ARCOS, CDC. Percent in Excess of Maximum Clinical Justifiable Opioid Use = (Actual MMEs Sold - Total Appropriate MMEs)/Actual MMEs Sold. Years for which epidemiological data was not available, linear estimation was used.

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FIGURE 6
MAXIMUM CLINICALLY JUSTIFIABLE OPIOID USES FOR
CANCER, TRAUMA AND SURGERY AND TOTAL MME SALES BY YEAR
(1993-2018)



Source: Actual MME Uses from IQVIA NPA, IPS, ARCOS, CDC. Appropriate Uses from AHRQ HCUP, CDC SEER, AHRF.

Note: Total Appropriate Use was calculated by summing predicted appropriate use if 100% of all cancer(deaths, CDC SEER), trauma (incidence, AHRQ HCUP), and surgery (inpatient and outpatient procedures, AHRF) were treated appropriately.

Cancer: daily dose = 80 MMEs/day, duration = 64 days. Surgery: daily dose = 30 MMEs/day, duration = 7 days. Trauma: daily dose = 30 MMEs/day, duration = 7 days.

102. The analysis described above can be applied at the county level. Table 7 shows comparable results for the Bellwether counties. Figure 7 likewise depicts the MMEs potentially clinically justified based on the same criteria as in the national analysis. Results in Table 4 and Figure 6 are provided for the years at issue in this case, 2006-2018.

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TABLE 7
SHARE OF SHIPMENTS OF PRESCRIPTION OPIOIDS (MME) JUSTIFIED BY CLINICAL CRITERIA

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Cuyahoga												
[1] Appropriate MMEs												
[2] Appropriate MMEs + 50%												
[3] Actual MMEs												
[4] Percent Appropriate												
Summit												
[1] Appropriate MMEs												
[2] Appropriate MMEs + 50%												
[3] Actual MMEs												
[4] Percent Appropriate												

Source: Epidemiological Data: AHRQ HCUP, CDC SEER, HRSA AHRF

Notes:

- 1 Appropriate MMEs = sum of MMEs needed to treat 100% of cancer, trauma and surgery cases given clinical parameters (Cancer: 80 MMEs/day over 64 days; Surgery and Trauma: 30 MMEs/day over 7 days)
- 2 Actual MMEs * 1.5.
- 3 Actual MMEs by County Provided by Compass Lexecon.
- 4 Percent Appropriate = Appropriate MMEs/Actual MMEs. [4] = [1]/[3].

Years for which epidemiological data was not available, linear estimation was used.

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FIGURE 7
MAXIMUM CLINICALLY JUSTIFIABLE OPIOID USES FOR
CANCER, TRAUMA AND SURGERY AND TOTAL MME SALES BY YEAR
FOR CUYAHOGA AND SUMMIT COUNTIES
(2006-2018)



Source: Actual MME Uses from Compass Lexecon (TBD). Appropriate Uses from AHRQ HCUP, CDC SEER, AHRF.

Note: Total Appropriate Use was calculated by summing predicted appropriate use if 100% of all cancer(deaths, CDC SEER), trauma (incidence, AHRQ HCUP), and surgery (inpatient and outpatient procedures, AHRF) were treated appropriately.
 Cancer: daily dose = 80 MMEs/day; duration = 64 days. Surgery: daily dose = 30 MMEs/day; duration = 7 days. Trauma: daily dose = 30 MMEs/day; duration = 7 days.

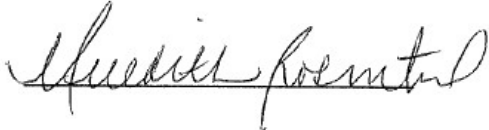
XI. SUMMARY AND CONCLUSIONS

103. In this Report, I have offered an economic framework that describes the incentives for pharmaceutical promotion and reviewed the literature demonstrating the impact of such promotion on sales. I also observe that the conclusions drawn from economic theory and empirical evidence are corroborated by deposition testimony and strategic documents obtained from Defendants. Using two alternative methods found in the published literature and comprehensive data on actual sales and promotion of opioids, I have quantified the impact of

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the alleged misconduct in this matter. These two approaches, which use different types of variation (time-series and cross-sectional) and data to identify the impact of Defendants' promotion, yield a range of impact estimates. The nesting of these results as predicted bolsters the reliability of each. In my opinion, given the limitations of data and the circumstances of opioid use and marketing over time, the results of the direct approach yield a lower bound of the causal relationship between the Defendant manufacturers' promotion on sales. Given that I also show that the growth of opioids cannot be explained by clinical need, the results of the indirect approach more closely reflect the relationship between the challenged conduct and opioid sales. Altogether, I find that promotion caused a large share of the sales of opioids nationally and in the Bellwether jurisdictions during the damage period. My estimates of the annual percentages of MMEs in the Bellwether jurisdictions for each year are adopted in Prof. Cutler's Report as an input to the calculation of harms caused by the alleged misconduct.

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A handwritten signature in cursive script, appearing to read "Meredith Rosenthal".

Prof. Meredith Rosenthal

March 25, 2019

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Attachment A

CURRICULUM VITAE

Date: March, 2019

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BIRTHPLACE: Boston, Massachusetts

EDUCATION:

1998 Health Policy (Economics track), Ph.D., Harvard University
1990 International Relations (Commerce), A.B., Brown University

ACADEMIC APPOINTMENTS:

2011-present C. Boyden Gray Professor of Health Economics and Policy
Department of Health Policy and Management
Harvard School of Public Health
2006-2011 Associate Professor of Health Economics and Policy
Department of Health Policy and Management
Harvard School of Public Health
1998-2006 Assistant Professor of Health Economics and Policy
Department of Health Policy and Management
Harvard School of Public Health

ADMINISTRATIVE APPOINTMENTS:

2017-2018 Senior Associate Dean for Academic Affairs
Harvard T. H. Chan School of Public Health
2013-2017 Associate Dean for Diversity
Harvard T. H. Chan School of Public Health

PROFESSIONAL SOCIETIES:

2014-present Elected Member, National Academy of Medicine (Institute of Medicine)
2004-present American Society of Health Economists
2000-present International Health Economics Association
1995-present AcademyHealth
Planning Committee for 2008 Annual Research Meeting

OTHER PROFESSIONAL EXPERIENCE:

1996-present Academic Affiliate, Greylock McKinnon Associates

1993-1994 Analyst, Health Economics Research, Inc./The Center for Health Economics Research

1990-1993 Consultant, Price Waterhouse, Tax Economics Department

SERVICE:

2016-present Member, Massachusetts Center for Health Information and Analysis Oversight Council

2013-2017 Board Chair, Massachusetts Health Quality Partners

2007-2016 Member, Massachusetts Public Health Council

2005 Expert Testimony, House Committee on Education and Workforce, House Subcommittee on Employer-Employee Relations, Hearing on Examining Pay-for-Performance Measures and Other Trends in Employer-Sponsored Health Care

2003 Expert Testimony, Senate Special Committee on Aging, Hearing on Direct to Consumer Advertising of Prescription Drugs: Exploring the Consequences

2001 Chair, Massachusetts Special Commission on Physician Compensation

HONORS AND DISTINCTIONS:

2016 AcademyHealth Paper of the Year Award

2016 Harvard TH Chan School of Public Health Student Mentoring Award

2015 Harvard TH Chan School of Public Health Advancement of Women Faculty Mentoring Award

2014 Harvard School of Public Health Junior Faculty Mentoring Award

2011 Harvard School of Public Health Teaching Citation

2010 Academy of Management Best Theory to Practice Paper in Health Care Management

2006 Alfred P. Sloan Foundation Industry Studies Fellowship

2003 Labelle Lectureship in Health Policy, McMaster University

MAJOR ADMINISTRATIVE RESPONSIBILITIES:

2016-2018 University President's Task Force on Inclusion and Belonging

2012-2014 Harvard School of Public Health Faculty Council, Vice-Chair (2012)

2007-2014 Harvard School of Public Health Committee on Admissions and Degrees, Chair (2010)

2007 Co-Chair, Harvard School of Public Health Child Care Task Force

2006-2011 Harvard School of Public Health Committee on the Concerns of Women Faculty

2000-present Executive Committee on Higher Degrees in Health Policy, Harvard University

1999-present Admissions Committee, Ph.D. Program in Health Policy, Harvard University

EDITORIAL ACTIVITIES:

1997-present Referee: *Journal of Health Economics, Inquiry, Health Services Research, Health Affairs, Journal of the American Medical Association, New England Journal of Medicine, and others*

2012-2015 Member, *New England Journal of Medicine*, Perspective Advisory Board

2008-2014 Associate Editor, Medical Care, Research and Review

1997-1998 Assistant Editor, Evidence-based Health Policy and Management

MAJOR RESEARCH INTERESTS:

1. Market-oriented health policy
2. Physician payment incentives
3. Consumerism and consumer-directed health plans
4. Economics of the pharmaceutical industry

RESEARCH SUPPORT:

Past Funding:

2015-2017 Improving the Value of Health Care Choices, Arnold Foundation, *Principal Investigator*

2012-2017 Optimizing Ambulatory Patient Safety in Partnership with Primary Care Transformation, HMS Gift/CRICO, *Co-Principal Investigator*

2016-2017 Physician Payment in ACOs, Arnold Foundation, *Principal Investigator*

- 2015-2020 Accelerating the Use of Evidence-based Innovations in Healthcare Systems, AHRQ, *Principal Investigator*
- 2013-2015 Understanding the Use and Impact of Price Data in Health Care, RWJF, *Co-Investigator*
- 2013-2015 Impact of Price Transparency Tools on Consumer Behavior, RWJF, *Co-Investigator*
- 2013-2015 Getting the Complete Picture: What Does the Body of Research on the Patient-Centered Medical Home Really Tell Us? CMWF, *Principal Investigator*
- 2013-2015 Prevalence and Variation in Over-Use of Health Services in Commercially Insured Patients, Peter G. Peterson Foundation, *Principal Investigator*
- 2013-2015 Measuring Overuse of Health Care: Are Providers and Patients ‘Choosing Wisely’?, CMWF, *Co-investigator*
- 2013-2014 Prevalence and Variation in Over-Use of Health Services in Medicare: Choosing Wisely, RWJF, *Co-investigator*
- 2012-2015 Evaluating Sequential Strategies to Reduce Readmission in Diverse Populations, AHRQ, *Co-investigator*
- 2010-2014 Factors Associated with Effective Implementation of a Surgical Safety Checklist, AHRQ (R18), *Co-investigator*
- 2010-2014 A Randomized Trial of Behavioral Economic Interventions to Reduce CVD Risk, NIA (RC4), *Co-investigator*
- 2008-2010 Rewarding Quality Diabetes Management, RWJF/Hudson Health Plan, *Principal Investigator*
- 2008-2009 Effects of High-Deductible Health Plans on Families with Chronic Conditions, RWJF/Harvard Pilgrim Healthcare Plan, *Co-Investigator*
- 2008-2008 Implications of Value-Based Purchasing for Health Disparities: A Synthesis of the Evidence, Office of Minority Health, Department of Health & Human Services, *Principal Investigator*
- 2008-2008 Payment Reform Opportunities for Medicaid Programs, University of Pittsburgh, *Principal Investigator*
- 2007-2009 Changes in Health Care Financing and Organization: How does Fragmentation of Care Contribute to the Costs of Care? RWJF/HCFQ, *Co-investigator*

- 2006-2008 Evaluating the Impact of a Novel Pay for Performance Program in a Medicaid Managed Care Plan, The Commonwealth Fund, *Principal Investigator*
- 2006-2008 Sloan Industry Studies Fellowship for Meredith Rosenthal, Alfred P. Sloan Foundation, *Principal Investigator*
- 2005-2008 Incentive Formularies and the Costs and Quality of Care, Agency for Healthcare Research and Quality, *Co-investigator*
- 2005-2007 Strategies to Improve the Value of Health Benefit Spending for Low-Wage Workers, The Commonwealth Fund, *Principal Investigator*
- 2005–2007 Uptake and Impact of Health Risk Appraisals, RWJ Health Care Financing and Organization Initiative, *Principal Investigator*
- 2003-2007 The Patterns and Impact of Value Based Purchasing, Agency for Healthcare Research and Quality, *Co-investigator*
- 2002-2007 Coverage, Organization of Care, and Colorectal Screening, National Institutes of Health, *Co-investigator*

Current Funding

- 2016-2018 Generic Drug Pricing: Actionable Research for Policy, Commonwealth Fund, *Principal Investigator*
- 2016-2021 Identifying Cascades of Low-Value Care and the Organizational Practices that Prevent Them, AHRQ, *Co-Investigator*
- 2016-2018 Generic Drug Pricing: Actionable Research for Policy, Commonwealth Fund, *Principal Investigator*

TEACHING EXPERIENCE

- 2016-present Health Policy and Management 260: Health Economics with Applications to Global Health Policy
- 2003-present Health Policy and Management 209: Economics for Health Policy
- 2013-2014 Global Health and Health Policy 50 (Harvard College): The Quality of Care in the United States
- 1999-2001 Health Policy and Management 507: Mental Health Economics and Policy in the United States

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Peer-Reviewed Articles

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18. **Rosenthal MB**, Frank RG, Li Z, and Epstein AM. Early experience with pay-for-performance: From concept to practice. *JAMA*. 2005 Oct 12;294(14):1788-93.
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21. **Rosenthal MB** and Frank RG. What is the empirical basis for paying for quality in health care? *Medical Care Research and Review*. 2006 April;63(2):135-57.
22. **Rosenthal MB** and Daniels NB. Beyond competition: The normative implications of consumer-driven health plans. *Journal of Health Politics, Policy, and Law*. 2006 Jun;31(3):671-86.
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Attachment B

**Attachment B
Materials Relied Upon**

Legal documents

21 C.F.R. §202.1.

21 C.F.R. §314.126.

21 U.S.C. §355(a)-(d).

Corrected Second Amended Complaint, *In Re National Prescription Opiate Litigation*, MDL No. 2804, Case No. 17-md-2804 (referring to Case No. 18-op-45090), United States District Court for the Northern District of Ohio Eastern Division, May 18, 2018.

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Deposition of Kimberly Deem-Eshleman, Janssen, in this matter, November 15, 2018.

Deposition of Phil Cramer, Purdue, in this matter, November 19, 2018.

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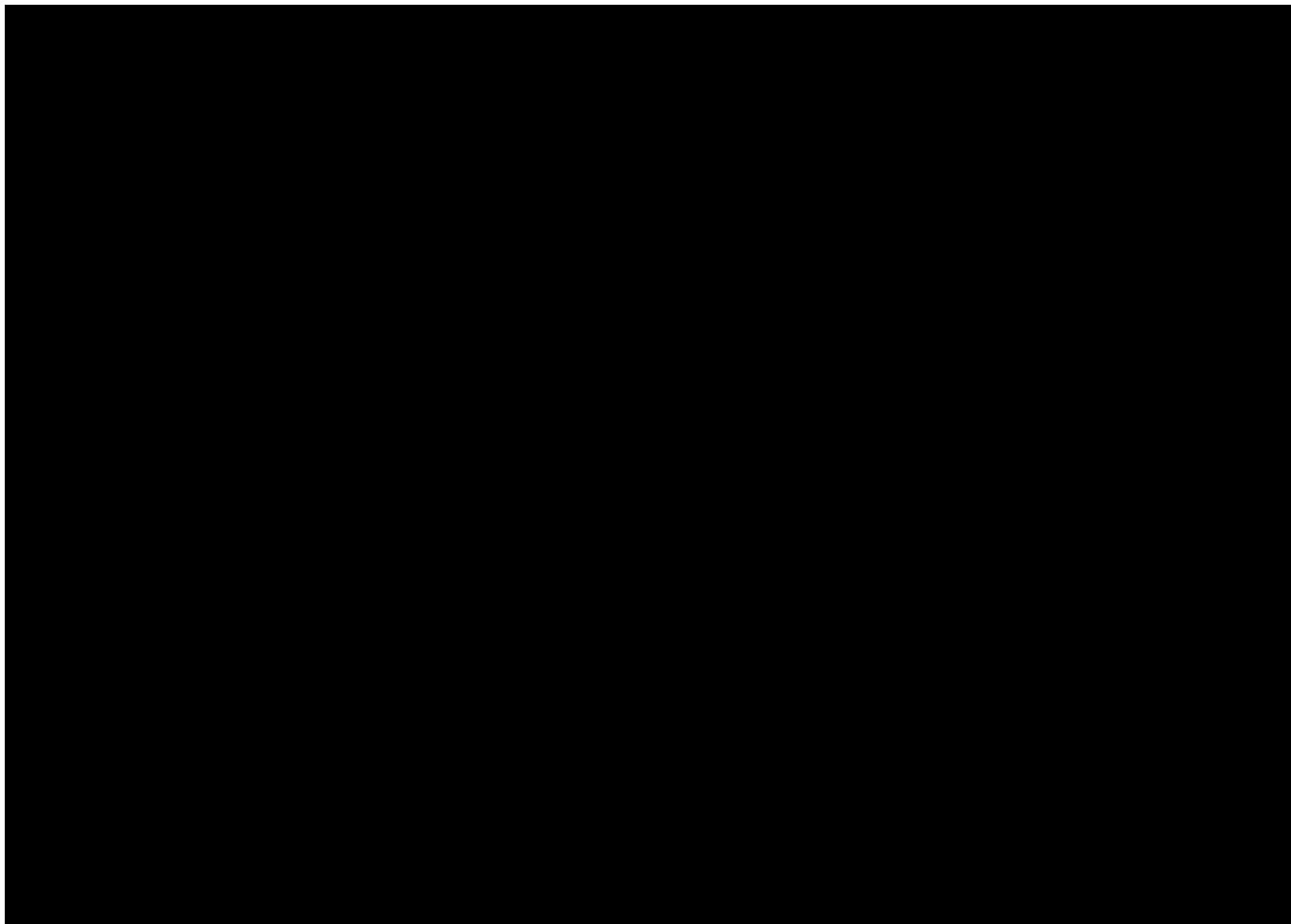
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Attachment C

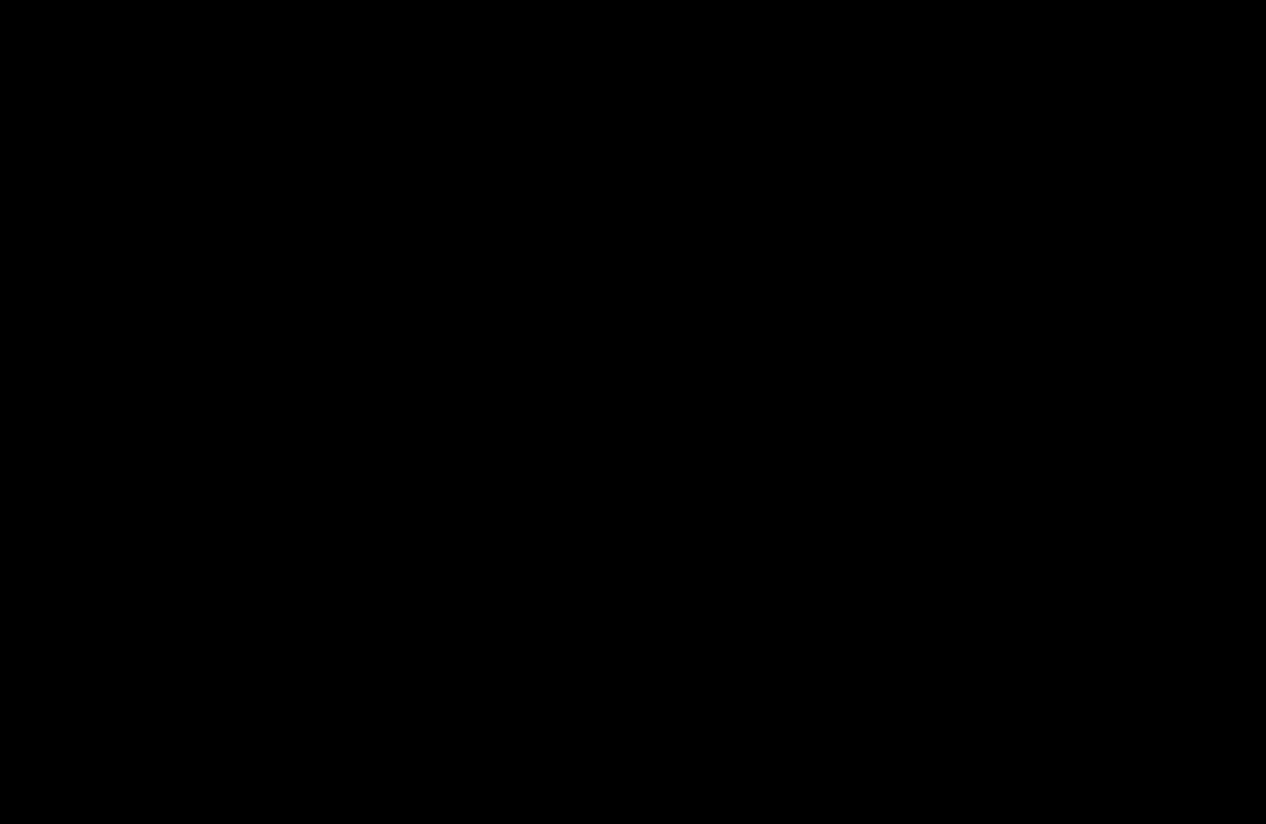
Table C.1

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018



Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018



Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Sales Period		Promotion	Wholesale	Retail	
Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

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Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

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Table C.2

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

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1993-2018

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Source: IQVIA NPA, IPA, ARCOS, CDC

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Source: IQVIA NPA, IPA, ARCOS, CDC

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Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.2

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

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Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
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Source: IQVIA NPA, IPA, ARCOS, CDC

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1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.3

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx

Source: IQVIA NPA, IPA, ARCOS, CDC

Table C.4

Defendant Opioid Drug Retail Sales and Promotion Summary
By Defendant
1993-2018

Defendant		Promotion		Sales			
Status	Defendant	Contacts	Percent	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.5

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status
1993-2018

Defendant	Manufacturer	Promotion		MME Sales			
Defendant	Manufacturer	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.5

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status
1993-2018

Defendant	Manufacturer	Promotion		MME Sales			
Defendant	Manufacturer	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.5

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status
1993-2018

Defendant	Manufacturer	Promotion		MME Sales			
Defendant	Manufacturer	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Pharmaceutical Acronyms

APAP: Acetaminophen; APC: Aspirin-Phenacetin-Caffeine; ASA: Asprin; CAF: Caffeine; DHC: Dihydrocodeine.

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

Table C.6

Summary of ARCOS Opioid Retail Sales and Promotion
By Defendant and Manufacturer Status, and Drug
1993-2018

Defendant	Manufacturer		Promotion		MME Sales			
Defendant	Manufacturer	Drug	Contacts	Percent Contacts	MME	Percent	EU TRx	Percent

Pha
APAP: Acetaminophen; APC: Aspirin-Phenacetin-Caffeine; ASA: Asprin; CAF: Caffeine; DHC: Dihydrocodeine.

Source: Source: IQVIA NPA, IPA, ARCOS, CDC. Class II oral opioids plus Butrans.

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Figure C.7

Total MME EUTRx Prescription Sales

Morphine Milligram Equivalents (MME) in millions



Source: IQVIA NPA, ARCOS, CDC.

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Attachment D

Attachment D

Technical Appendix

I. Direct Approach

The basic form of an aggregate model of the effect of promotion on total opioid MME sales is:

$$Q_t = \alpha_0 + \beta_0 S_t + \sum \gamma_j X_{jt} + \varepsilon_t \quad (\text{D.1})$$

$$S_t = (1 - \delta_0) S_{t-1} + D_t \quad (\text{D.2})$$

Where:

Q_t is the quantity of opioids prescribed in period t measured by morphine milligram equivalents (MME).

D_t is the current flow of marketing activities for opioids in period t .

S_t is the aggregate stock of marketing activities for opioids in period t . This includes promotion measured as the number of detailing contacts.¹

X_{jt} is a set of time-varying factors hypothesized to impact prescribing.

Data Sources

The main source of data used for the direct analysis is data vendor IQVIA, in particular its National Prescription Audit (NPA) Retail Data, National Sales Perspective (NSP) Wholesale data, and Integrated Promotional Services (IPA) on drug promotion. There are no reports of contacts for Purdue for OxyContin during the 24-month period January 2001 through December 2002. Based on information

¹ Note that the promotion stock variable is recursive; for example, in first period it is $S_1 = D_1$, in the second period it is $S_2 = (1 - \delta_0) D_0 + D_2$, in the third period it is $S_3 = (1 - \delta_0)^2 D_1 + (1 - \delta_0) D_2 + D_3$, etc. As the parameter δ_0 is part of the estimation process and enters the model nonlinearly, the model cannot be estimated using ordinary least squares. In early academic work that used the concept of depreciating capital stock of promotion, the depreciation rate was estimated using a grid search. (See E. Berndt, L. Bui, D. Lucking-Reiley, G. Urban, "The Roles of Marketing, Product Quality, and Price Competition in the Growth and Composition of the U.S. Antiulcer Drug Industry," in T. Bresnahan and R. Gordon, *The Economics of New Goods*, Chicago: University of Chicago Press for the NBER, 1996, pp. 277-328). The statistical package I used for this estimation, SAS v9.4 has the capability to estimate non-linear models that use lags of the form used in this model (via the command "proc model") and is able to estimate the standard errors for the depreciation parameter, δ_0 .

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provided through discovery, Purdue reported the monthly detail calls for OxyContin from January 1999 to November 2002.² These monthly sales calls overlapped with reported IQVIA detailing contacts. A statistical relationship between Purdue data and IQVIA data was determined and used to predict the missing IQVIA contacts.

IQVIA IPS did not report detailing contacts by physician specialty in 2011, but it did report total contacts for each month. The distribution of contacts across specialties was determined in adjacent months for each manufacturer and drug. When sufficient information was available, the distribution of contacts across specialties was calculated. In instances where manufacturers only promoted a drug in 2011, the distribution of contacts across specialties was obtained from all manufacturers that promoted for that drug.

This same technique was used to determine the distribution of Purdue sales calls across physician specialties in 2001 and 2002.

The ARCOS shipments data were provided to me by Compass-Lexecon.³

Extended units were converted to morphine milligram equivalents using information from the U.S. Centers for Disease Control⁴ and Excellus Blue Cross Blue Shield.⁵

Drugs Included in the Case

The drugs included in this analysis are limited to the drugs identified in ARCOS shipments data that were also found in IQVIA National Perspective Audit (NPA) retail prescription data. The drugs were matched by National Drug Code (NDC) where possible, or otherwise on standardized drug name matches. Injectable drugs were excluded while all other forms of opioid drugs were included. All buprenorphine drugs were excluded, except for Butrans. The list of drugs was further limited to those that were ever classified as

² See OxyContin, State of the Brand, January 2003, PKY182070977.pdf PKY182070977 at 989.

³ US ARCOS Total Shipments by NDC Code.xlsx.

⁴ CDC, "Data Resources: Analyzing Prescription Data and Morphine Milligram Equivalents (MME)" (Excel spreadsheet available at <https://www.cdc.gov/drugoverdose/resources/data.html>).

⁵ "Summary of Opioid POS for CY19" (https://www.excellusbcbs.com/wps/wcm/connect/4c541bc8-d8e2-41a1-9bba-83bbe1516ba6/Medicare+D+Formulary-Level+Cumulative+Opioid+and+Opioid++Buprenorphine+POS+Edits_03_01_2018.pdf?MOD=AJPERES&CACHEID=4c541bc8-d8e2-41a1-9bba-83bbe1516ba6).

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DEA Class II, except for Butrans, which is a DEA Class III drug. Based on information from the CDC, the milligram morphine equivalent (MME) was computed for each drug. The list of drugs used in this analysis is shown in Attachment C, Table C.1.

Data Descriptions

The aggregate national MME sales show the MME sales from all of the drugs shown in Table C.1. These drugs are manufactured and promoted by the Defendants and other non-Defendants. More detailed summaries of manufacturer and drug specific sales and promotion information are given in Tables C.2 and C.3.

Changes in the Effectiveness of Promotion

The factors that contributed to the growth, acceleration in growth, and the ultimate drop in sales are described in the main text. See Figure D.1 below.

The model specification of interest estimates the impact of changes in aggregate marketing on sales. The impact of marketing on sales has typically been estimated as a single coefficient that is assumed to be constant over the estimation period. The baseline model in equation (D.1) is specified assuming a constant impact of promotion, β_0 . However, empirical evidence indicates that the return to a change in the stock of detailing varies over the 1993-2018 period.

An empirical model of the return to marketing may capture the net return based on pharmaceutical marketing stock in conjunction with all countervailing efforts that influence physician prescribing behavior. These influences change over time and three alternative specifications are considered below. Each of the models below includes an aggregate price index for opioids in X which represents additional explanatory variables.

$$Q_t = \alpha_0 + \beta_0 S_t + \theta_0 X_t + \varepsilon_t \quad \text{Model A (D.3)}$$

$$Q_t = \alpha_0 + (\beta_1 D_1 + \beta_2 D_2 + \beta_3 DT_3) S_t + \theta_0 X_t + \varepsilon_t \quad \text{Model B (D.6)}$$

$$Q_t = \alpha_0 + (\beta_1 D_1 + \beta_2 D_2 + \beta_3 DT_3) S_t + \sum \theta_{0j} X_{jt} + \varepsilon_t \quad \text{Model C (D.5)}$$

Where:

Model A: α_0 , β_0 , θ_0 and δ_0 are coefficients to be estimated

Model B α_0 , β_1 , β_2 , β_3 , θ_0 and δ_0 are estimated, D_1 is a dummy with value=1 prior to March 2002 and equal to 0 starting March 2002; D_2 is a dummy with value=0 prior to March

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2002 and equal to 1 starting March 2002; and DT_3 is a dummy trend 0 prior to August 2010, 1 starting August 2010 and increments by 1 for each month thereafter

Model C Same parameters definitions as Model C, adding explanatory variables to account for the potential influence of events. In this model a set of six explanatory variables is represented by the matrix X. These are the price index plus five dummy variables to account for events.

Model A does not allow for a change in the effectiveness of promotion. Models B and C allow for two changes in the effectiveness of promotion. In all models include rate of depreciation, δ_0 , for the stock of promotion that is constant throughout the period 1993-2018.

The econometric results from estimating equation D.3 and Model A are shown below in Table D.1; the predicted values are shown in Figure D.1. The results from estimating equation D.2 and Model B which accounts for the change in effectiveness at two points in time are shown in Table D.2 and the predicted values are shown in Figure D.2. Model C is shown in Table D.3 and Figure D.3.

Aggregate Price Index for Opioids

A Fisher ideal price index was used as the measure of prices of the opioid drugs in the model. The Fisher ideal is a well-regarded price-index method that takes into account changes in product composition and characteristics over time.⁶ It is used by the U.S. Bureau of Economic Analysis to estimate changes in pharmaceutical prices over time, adjusting for changes in product attributes and quality.⁷ The price index was constructed using monthly data on the dollar value of sales and quantity of extended units for each drug/form/strength combination in the data. I followed standard procedures to account for the entry of new drugs and exit of drugs by including in the index calculation for a given period only those drug/form/strength combinations that were present in two consecutive months.

⁶ A. Aizcorbe and N. Nestoriak, "Changing mix of medical care services: Stylized facts and implications for price indexes," *Journal of Health Economics*, 30(3), 2011, pp. 568-574. A. Aizcorbe and N. Nestoriak, "Price Indexes for Prescription Drugs: A Review of the Issues," in *Oxford Handbook of the Economics of the Biopharmaceutical Industry*, eds., P. Danzon and S. Nicholson, Oxford, UK: Oxford University Press, 2012, pp. 438-462.

⁷ A. Dunne, S. Grosse and S. Zuvekas, "Adjusting Health Expenditures for Inflation: A Review of Measures for Health Services Research in the United States," *Health Services Research*, 53(1), 2016, pp.175-196.

Determining Turning Points in Effectiveness of Promotion

In Model B the two dates that would delineate the early and late change in the effectiveness of promotional stock were determined through a two-dimension search. The first turning point was chosen between January 1999 and January 2003; and the second turning point was chosen with the date between January 2010 to December 2011. There are 1,176 combinations of these two months, so the model is estimated 1,176 times. The date combination with the best fit, defined as the greatest Wald statistic was April 2002 and September 2010. Model C used the same turning points as found in Model B.

Separate from marketing efforts, there are other factors that could potentially influence the sales of opioids. While marketing to physicians is one important explanation for changes in sales, and the use of dummy variables captures broad factors that influence the market for opioids, there could still be factors that influence physicians to write prescriptions and consumers in their willingness to fill prescriptions for opioids. To test the robustness of the Model C I used the same turning points and introduce five events into the model. These events are identified here:

- dd_jan1998_APPM_APS Consensus Statement From AAPM/APS 01/1998
- dd_jan1999_FSMBG Federation of State Medical Boards Guidelines 01/1999
- dd_jan2001_JCAHO JCAHO pain standards releases 01/2001
- dd_Aug2010_OxyContin OxyContin Reformulation 08/2010
- dd_oct2014_hydro_resched Hydrocodone Rescheduling 10/2014"

My *a priori* expectation is that the first three events would have a positive impact on the quantity of MMEs prescribed per month. The reformulation of OxyContin could have an ambiguous impact on MME sales. On one hand, the new reformulation was intended to make it more difficult to use the drug for illicit purposes; for that reason, it could reduce MME sales (to the extent that diversion was prevalent.) On the other hand, physicians could be less hesitant to prescribe the drug since they were assured that it would be less likely to be used illicitly. The impact of rescheduling hydrocodone from Class III to Class II could result in a reduction of MME sales.

The results from estimating this model are shown in Table D.3 and the predicted values are shown in Figure D.3. The signs of the coefficients on the event dummies did not conform to my *a priori* expectations. The sign on the consensus statement was negative which is directly at odds with the intension of the consensus statement. While two coefficients were statistically significant, as a group they were jointly insignificant.

Sensitivity tests

Additional sensitivity tests were conducted based on my preferred Model B. Beginning with Model B, I considered a time trend as an alternative to the price index. The time trend incremented by 1 for each month after January 1993. As shown in Table D.6, the time trend is not statistically significant at 5% level of significance, and it does not have a material impact on the other parameter estimates and the measure of harm. Moreover, the introduction of a time trend is not an appropriate explanatory variable when one is trying to explain the cause of a trend as opposed to trying to exclude the impact of the trend. In this empirical exercise, the objective is to try and explain the cause of the trends, so I would prefer not to detract from the explanatory power of promotional efforts.

Alternative Dependent Variable

The total number of extended units (*i.e.*, pills) dispensed at the retail level was also considered as a dependent variable. As MMEs are computed from extended units (converted to morphine milligram equivalents), the two are very closely related (as shown in Figure 2 of my report). The turning points for Model B and C were determined using the same methods as described above. Results are shown in Table D.7 through D.9 and Figure D.6 through D.8.

But-For Calculations

The measure of harm is determined based on the estimated parameters for each of the models. The number of detailing contacts that are alleged to be tainted by misconduct are removed from the aggregate measure of contacts. The stock of promotion is then recomputed using the estimated parameter values for δ_0 . The measure of harm is then computed as the difference between predicted actual dependent variable and the predicted dependent variable with the but-for assumptions imposed.

Comcast Considerations

The calculation of impact due to misconduct can be readily revised to conform to any ruling by the court. For example, if, for some reason, a specific Defendant was exempted from liability because their marketing messages were not found to be unlawful, then the measure of harm can be updated to include that Defendants' promotion in the but-for – and lawful promotion. This is shown in Table 3 of the main report. This same technique can be used to account for changes that exempt for liability at a specific point in time, that exempt promotion to specific physician specialties, or for promotion for specific drugs. Any combination of these considerations can be accommodated with the analysis developed here.

II. Indirect Approach

The indirect approach undertakes an analysis of “excess shipments” of opioids over the period 1995-2016. This analysis assumes that per capita consumption of opioids prior to 1997 is untainted by Defendant fraudulent marketing. The pattern of consumption is modeled across large counties in the US and then this level of use is extended forward in time based on changes in demographic characteristics. The impact of prices is also accounted for through the inclusion of a price index.

Estimates of “but for” shipments are based on: (i) the relationship between MMEs per capita and county characteristics observed in 1997, and (ii) changes in the demographic/economic characteristics of counties over time. The analysis begins with a measure of “but for” shipments accounts for trends in per capita shipments prior to the period of Defendants’ alleged misconduct.

This indirect approach assumes that MMEs per capita would grow based at a rate reflecting the average annual growth in shipments from 1980-1995 as reported by the International Narcotics Control Board. These data are available for the U.S. as whole and are comparable for national estimates of MME per capita from ARCOS.

The year 1997 is used as the benchmark period because it is the first for which shipment data are available from ARCOS. Because Defendants’ misconduct elevated 1997 shipments above “but for” levels, this approach yields a conservative estimate of excess shipments.

IQVIA data is used to estimate the conversion to an earlier benchmark year, by incorporating an adjustment to these results to reflect changes in shipments between 1995 and 1997.

The relationship between MMEs per capita and county characteristics is estimated using the large county sample used in the mortality analysis.

Indirect Regression model

A regression model generates estimates of the relationship between MMEs per capita in a county (the dependent variable), and a variety demographic and economic characteristics of sample counties in 1997. These explanatory variables include: the distribution of area population by age, race, gender, and educational attainment; labor force participation and unemployment in the area; the distribution of area employment by major industry; county population; the percent of county population living in urban areas; and the county’s poverty rate, cancer deaths and prevalence of uninsured.

“But for” estimates of MMEs per capita for subsequent years are generated based on the regression estimates and changes over time in the economic and demographic characteristics of sample counties. The results of the regression analysis are shown in the main report in Table. The calculated harms are reported in Table

Data Sources

The main data sets used for this analysis are as follows:

- | | |
|--|--|
| • INCB Opioid Consumption Data.xlsx | U.N. International Narcotics Control Board |
| • County level demographic information | AHRQ Area Hospital Research File |
| • Opioid shipments data | ARCOS data provided by Compass-Lexecon |
| • Cancer controls | Center for Disease Control |
| • Indirect regression data | Demographic information |
| • Mortality rates | Center for Disease Control |

III. Appropriate Use Analysis

The Appropriate Use Analysis estimated the demand in MMEs of appropriate opioid use for (1) end-of-life cancer care, (2) acute post-surgical care, and (3) ER trauma incidents. National and county-level analyses were performed separately due to data availability.

A. National-Level

Cancer: cancer mortality data were acquired from Surveillance, Epidemiology, and End Results (SEER), Centers for Disease Control and Prevention (CDC) [deaths/100,000 persons] and multiplied by total population/100,000 by year to calculate number of cancer deaths by year. See Table D (a). Data was available for 1980-2015. Daily MME dose was assigned as 80 MMEs/day. Treatment duration was assigned as 64 days/death. Duration was calculated from the average of studies, weighted by sample size, discussed in Carlson (2016).⁸ Studies were selected if they reported both the sample size and the average duration of treatment. MMEs/year for cancer was then calculated as cancer deaths * treatment duration * daily dose.

⁸ Carlson, Cathy. “Effectiveness of the World Health Organization Cancer Pain Relief Guidelines: An Integrative Review.” *Journal of Pain Research*, Volume 9, 2016, pp. 515–534.

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Table D (a)
National Cancer Mortality

Year	[1]	[2]	
	Death Rate [/100,000]	Population	# deaths
1995	209.89	266,278,400	558,892
1996	207	269,394,300	557,646
1997	203.55	272,646,900	554,973
1998	200.82	275,854,100	553,970
1999	200.72	279,040,200	560,089
2000	198.79	282,162,400	560,911
2001	196.29	284,969,000	559,366
2002	194.36	287,625,200	559,028
2003	190.89	290,107,900	553,787
2004	186.84	292,805,300	547,077
2005	185.23	295,516,600	547,385
2006	182.03	298,379,900	543,141
2007	179.26	301,231,200	539,987
2008	176.32	304,094,000	536,179
2009	173.4	306,771,500	531,942
2010	171.74	309,349,700	531,277
2011	168.74	311,644,300	525,869
2012	166.34	313,993,300	522,296
2013	163.19	316,234,500	516,063
2014	161.3	318,622,500	513,938
2015	158.68	321,039,800	509,426

SOURCES and NOTES:

1 Deaths rates from SEER, CDC.

2 #deaths = death rate * population/1000,000

Trauma:

Trauma incidence was identified as national emergency department trauma/injury incidents from the Health Care Utilization Project (HCUP), Agency on Healthcare Research and Quality (AHRQ). Trauma and injury are classified by the Clinical Classification System (CCS) codes: 2601-2611, 2614. These codes encompass all ICD-9 codes for External cause of injury (E codes) except those for poisoning, overexertion, suffocation, adverse effects of medical care/drugs, and other or unspecified causes. Data was available for 2006-2014. Daily MME dose was assigned as 30 MMEs/day. Treatment duration was assigned as 7 days/incident. MMEs/year for trauma was then calculated as trauma incidents * treatment duration * daily dose. MMEs/year in years for which epidemiological data were missing then were modeled using previously calculated MMEs/year data.

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Surgery:

Surgical procedures were identified as both inpatient and outpatient short-term general and short-term non-general (general v. non-general refers to hospital type) from the Area Health Resource File (AHRF), Health Resources & Services Administration (HRSA). Data was available for 2005, 2010, and 2014. These included AHRF variables: f0958705, f0958710, f0958714 (Total Surgery STG), and f0958905, f0958910, f0958914 (Total Surgery STNG). The number of total surgeries in-between available years were calculated by linear imputation (2006-2009 and 2011-2013). Shown in Table D (b).

Table D (b)

Surgery Imputation for Number of Operations Nationally

	[1]	[2]	[3]		[4]	[5]	[6]		[7]	[8]	[9]
Year	Inpatient Surgery STG	Inpatient Surgery STNG	Total Inpatient		Outpatient Surgery STG	Outpatient Surgery STNG	Total Outpatient		Total Surgery STG	Total Surgery STNG	Total Surgery
2005	9,993,160	489,916	10,483,076		17,272,265	1,152,442	18,424,707		27,265,425	1,642,358	28,907,783
2006	9,966,097	488,955	10,455,052		17,268,204	1,162,480	18,430,685		27,234,301	1,651,435	28,885,736
2007	9,939,034	487,994	10,427,028		17,264,143	1,172,519	18,436,662		27,203,177	1,660,513	28,863,690
2008	9,911,970	487,033	10,399,003		17,260,083	1,182,557	18,442,640		27,172,053	1,669,590	28,841,643
2009	9,884,907	486,072	10,370,979		17,256,022	1,192,596	18,448,617		27,140,929	1,678,668	28,819,597
2010	9,857,844	485,111	10,342,955		17,251,961	1,202,634	18,454,595		27,109,805	1,687,745	28,797,550
2011	9,629,276	468,863	10,098,139		17,214,348	1,244,638	18,458,986		26,843,624	1,713,501	28,557,125
2012	9,400,709	452,615	9,853,323		17,176,735	1,286,643	18,463,377		26,577,443	1,739,257	28,316,700
2013	9,172,141	436,366	9,608,507		17,139,121	1,328,647	18,467,768		26,311,262	1,765,013	28,076,275
2014	8,943,573	420,118	9,363,691		17,101,508	1,370,651	18,472,159		26,045,081	1,790,769	27,835,850

SOURCES and NOTES:

Data from the Area Health Resource File (AHRF)

1 AHRF variables: f0958305, f0958310, f0958314. STG = Short Term General Hospital

2 AHRF variables: f0958405, f0958410, f0958414. STNG = Short Term Non-General Hospital

3 Total Inpatient = Inpatient STG + Inpatient STNG

4 AHRF variables: f0970705, f0970710, f0970714

5 AHRF variables: f0958605, f0958610, f0958614

6 Total Outpatient = Outpatient STG + Outpatient STNG

7 AHRF variables: f0958705, f0958710, f0958714

8 AHRF variables: f0958905, f0958910, f0958914

9 Total Surgery = Total Surgery STG + Total Surgery STNG

Values calculated by linear imputation

f09583(05,10,14) = Surgical Operations, Inpatient Short Term General Hospitals (2005, 2010, 2014)

f09584(05,10,14) = Surgical Operations, Inpatient ST Non-Gen + Long Term Hosps (2005, 2010, 2014)

f0707(05,10,14) = Surgical Operations, Outpatient Short Term General Hospitals (2005, 2010, 2014)

f09586(05,10,14) = Surgical Operations, Outpatient ST Non-Gen + Long Term Hosps (2005,2010,2014)

f09587(05,10,14) = Surgical Operations, Total Short Term General Hospitals (2005,2010,2014)

f09589(05,10,14) = Surgical Operations, Total ST Non-Gen + Long Term Hosps (2005,2010,2014)

User Documentation for the County Area Health Resource File (AHRF) 2016-2017 Release defines Surgical Operations and Operating Rooms within Utilization on pg 67: 2005, 2010 and 2014 number of Surgical Operations by Patient Status (i.e., inpatient versus outpatient) are tallied for short term general hospitals, and short term non-general and long term hospitals which were open in each of the respective years. Number of Surgical Operations are available for Veterans hospitals which were open in 2014. Number of Operating Rooms are available for short term general hospitals and short term non-general and long term hospitals for 2005, 2010 and 2014.

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Daily MME dose was assigned as 30 MMEs/day. Treatment duration was assigned as 7 days/incident. MMEs/year for surgery was then calculated as surgical procedures * treatment duration * daily dose. MMEs/year in years for which epidemiological data were missing then were modeled using previously calculated MMEs/year data.

Total Appropriate MMEs were then summed across cancer, trauma, and surgery by year. Total Appropriate MMEs were then multiplied by 1.5 to account for potential underestimation of the data or treatment variables (treatment duration or daily dose).

Total Actual MMEs prescribed were summed by year from the regression data (see Data).

B. County-Level (Cuyahoga and Summit)

Cancer: annual cancer mortality data by county for Cuyahoga and Summit were received from Compass-Lexecon. Data was available for 1992-2016. Daily MME dose and treatment duration were again 80 MMEs/day for 64 days. MMEs/year for cancer was then calculated as cancer deaths * treatment duration * daily dose. MMEs/year in years for which epidemiological data were missing then were modeled using previously calculated MMEs/year data.

Trauma: trauma incidence was identified as national emergency department trauma/injury incidents from the Health Care Utilization Project (HCUP), Agency on Healthcare Research and Quality (AHRQ). Trauma and injury were again classified by the CCS codes: 2601-2611, 2614. Trauma incidents/100,000 persons nationally were then multiplied by county populations/100,000 persons by year to estimate county-level trauma incidents.

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Table D (c)

Trauma Estimation for Number of Trauma ER Visits in Cuyahoga and Summit, OH.

Year	[1] Visits/100,000 persons	[2] Cuyahoga Pop	[3] Summit Pop	[4] Cuyahoga trauma [visits]	[5] Summit trauma [visits]	[6] Total Trauma [visits]
2006	6,761.5	1,314,241	545,931	88,862	36,913	125,776
2007	6,734.4	1,295,958	543,487	87,275	36,601	123,876
2008	6,800.1	1,283,925	542,562	87,308	36,895	124,203
2009	6,723.8	1,275,709	542,405	85,776	36,470	122,246
2010	6,867.2	1,280,122	541,781	87,909	37,205	125,114
2011	6,719.4	1,270,294	539,832	85,356	36,273	121,630
2012	6,800.1	1,265,111	540,811	86,029	36,776	122,805
2013	6,611.9	1,263,154	541,824	83,518	35,825	119,343
2014	6,692.8	1,259,828	541,943	84,318	36,271	120,589

Calculated Value**SOURCES and Notes:**

- 1 HCUP, AHRF
- 2 Area Health Resource File (AHRF) County code 39035
- 3 Area Health Resource File (AHRF) County code 39153
- 4 Cuyahoga trauma = (Visits/100,000 persons)*(Cuyahoga Pop)/100,000. [4]=[1]*[2]/100,000
- 5 Summit trauma = (Visits/100,000 persons)*(Summit Pop)/100,000. [5]=[1]*[3]/100,000
- 6 Total Trauma = Cuyahoga trauma + Summit Trauma. [6]=[4]+[5]

Daily MME dose and treatment duration were again 30 MMEs/day for 7 days. MMEs/year for trauma was then calculated as trauma incidents * treatment duration * daily dose. MMEs/year in years for which epidemiological data were missing then were modeled using previously calculated MMEs/year data.

Surgery:

Surgical procedures were identified as both inpatient and outpatient short-term general and short-term non-general from AHRF, HRSA. Data was available for 2005, 2010, and 2014. These included AHRF variables: f0958705, f0958710, f0958714 (Total Surgery STG), and f0958905, f0958910, f0958914 (Total Surgery STNG) for AHRF county codes 39035 (Cuyahoga) and 39153 (Summit). The number of total surgeries in-between available years were calculated by linear imputation (2006-2009 and 2011-2013). Daily MME dose and treatment duration were again 30 MMEs/day for 7 days. MMEs/year for surgery was then calculated as surgical procedures * treatment duration * daily dose. MMEs/year in years for which epidemiological data were missing then were modeled using previously calculated MMEs/year data.

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Total Appropriate MMEs were then summed across cancer, trauma, and surgery by year. Total Appropriate MMEs were then multiplied by 1.5 to account for potential underestimation of the data or treatment variables (treatment duration or daily dose).

Data Sources:

- Surveillance, Epidemiology, and End Results (SEER), Centers for Disease Control and Prevention (CDC).
- Health Care Utilization Project (HCUP), Agency on Healthcare Research and Quality (AHRQ).
- Area Health Resource File (AHRF), Health Resources & Services Administration (HRSA).
- Direct Regression data Model B (see Data section, IQVIA NPA, IQVIA NSP, ARCOS, CDC)
- Total Actual MMEs shipped were received from Compass-Lexicon.

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Table D (d)

Surgery Imputation for Number of Operations in Cuyahoga and Summit, OH.

Surgery Imputation for Number of Operations in Cuyahoga									
Year	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]
	Inpatient Surgery STG	Inpatient Surgery STNG	Total Inpatient	Outpatient Surgery STG	Outpatient Surgery STNG	Total Outpatient	Total Surgery STG	Total Surgery STNG	Total Surgery
2005	85911	65	85,976	171,234	149	171,383	257,145	214	257,359
2006	86,345	75	86,420	172,124	214	172,338	258,468	290	258,758
2007	86,778	86	86,864	173,013	279	173,293	259,791	365	260,157
2008	87,212	96	87,308	173,903	345	174,247	261,115	441	261,555
2009	87,645	107	87,752	174,792	410	175,202	262,438	516	262,954
2010	88079	117	88,196	175682	475	176,157	263,761	592	264,353
2011	86,702	91	86,793	182,107	700	182,807	268,809	791	269,599
2012	85,325	65	85,389	188,532	925	189,457	273,857	989	274,846
2013	83,947	38	83,986	194,957	1,149	196,106	278,904	1,188	280,092
2014	82570	12	82,582	201,382	1,374	202,756	283,952	1,386	285,338

Surgery Imputation for Number of Operations in Summit									
Year	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]
	Inpatient Surgery STG	Inpatient Surgery STNG	Total Inpatient	Outpatient Surgery STG	Outpatient Surgery STNG	Total Outpatient	Total Surgery STG	Total Surgery STNG	Total Surgery
2005	19151	3,005	22,156	30,293	11,143	41,436	49,444	14,148	63,592
2006	18,111	3,010	21,121	30,101	11,578	41,680	48,213	14,588	62,801
2007	17,072	3,015	20,086	29,910	12,014	41,924	46,982	15,028	62,010
2008	16,032	3,019	19,052	29,718	12,449	42,167	45,750	15,469	61,219
2009	14,993	3,024	18,017	29,527	12,885	42,411	44,519	15,909	60,428
2010	13,953	3,029	16,982	29,335	13,320	42,655	43,288	16,349	59,637
2011	14,011	3,152	17,163	28,919	13,208	42,127	42,929	16,360	59,289
2012	14,068	3,275	17,343	28,502	13,097	41,599	42,570	16,372	58,942
2013	14,126	3,398	17,524	28,086	12,985	41,070	42,211	16,383	58,594
2014	14,183	3,521	17,704	27669	12,873	40,542	41,852	16,394	58,246

SOURCES and NOTES:

Data from the Area Health Resource File (AHRF) for county codes Cuyahoga (39035), and Summit (39153)

- 1 AHRF variables: f0958305, f0958310, f0958314. STG = Short Term General Hospital
- 2 AHRF variables: f0958405, f0958410, f0958414. STNG = Short Term Non-General Hospital
- 3 Total Inpatient = Inpatient STG + Inpatient STNG
- 4 AHRF variables: f0970705, f0970710, f0970714
- 5 AHRF variables: f0958605, f0958610, f0958614
- 6 Total Outpatient = Outpatient STG + Outpatient STNG
- 7 AHRF variables: f0958705, f0958710, f0958714
- 8 AHRF variables: f0958905, f0958910, f0958914
- 9 Total Surgery = Total Surgery STG + Total Surgery STNG

Values calculated by linear imputation

f09583(05,10,14) = Surgical Operations, Inpatient Short Term General Hospitals (2005, 2010, 2014)
 f09584(05,10,14) = Surgical Operations, Inpatient ST Non-Gen + Long Term Hosps (2005, 2010, 2014)
 f09707(05,10,14) = Surgical Operations, Outpatient Short Term General Hospitals (2005, 2010, 2014)
 f09586(05,10,14) = Surgical Operations, Outpatient ST Non-Gen + Long Term Hosps (2005,2010,2014)
 f09587(05,10,14) = Surgical Operations, Total Short Term General Hospitals (2005,2010,2014)
 f09589(05,10,14) = Surgical Operations, Total ST Non-Gen + Long Term Hosps (2005,2010,2014)

User Documentation for the County Area Health Resource File (AHRF) 2016-2017 Release defines Surgical Operations and Operating Rooms within Utilization on pg. 67: 2005, 2010 and 2014 number of Surgical Operations by Patient Status (i.e., inpatient versus outpatient) are tallied for short term general hospitals, and short term non-general and long term hospitals which were open in each of the respective years. Number of Surgical Operations are available for Veterans hospitals which were open in 2014. Number of Operating Rooms are available for short term general hospitals and short term non-general and long term hospitals for 2005, 2010 and 2014.

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Table D (e)**Epidemiological Data Used for Appropriate Use Analysis**

Year	Cancer Cuyahoga	Cancer Summit	Surgery Cuyahoga	Surgery Summit	Trauma Cuyahoga	Trauma Summit
1995	3,787	1,284				
1996	3,756	1,243				
1997	3,645	1,158				
1998	3,604	1,252				
1999	3,613	1,183				
2000	3,584	1,257				
2001	3,570	1,243				
2002	3,418	1,265				
2003	3,372	1,259				
2004	3,468	1,259				
2005	3,370	1,213	257,359	63,592		
2006	3,189	1,204	258,758	62,801	88,862	36,913
2007	3,244	1,281	260,157	62,010	87,275	36,601
2008	3,210	1,216	261,555	61,219	87,308	36,895
2009	3,039	1,259	262,954	60,428	85,776	36,470
2010	3,158	1,220	264,353	59,637	87,909	37,205
2011	3,096	1,234	269,599	59,289	85,356	36,273
2012	3,167	1,154	274,846	58,942	86,029	36,776
2013	2,997	1,147	280,092	58,594	83,518	35,825
2014	2,998	1,269	285,338	58,246	84,318	36,271
2015	2,948	1,257				
2016	3,062	1,218				

Sources: SEER CDC, HCUP AHRQ, AHRF HRSA.

Table D.1

MME_EUTRX: Baseline Model: Single, Constant Estimate of Promotional Effectiveness with Price Index
No Events or Turning Pointst

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
mme_eutrx							

Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b					
x					
main0					

Source: IQVIA (NPA, IPA), ARCOS, CDC.

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Figure D.1

Actual, Predicted Actual, and Predicted But-For MME EUTRx with Baseline Model

$$\text{MME_EUTRX} = (a) + (b) * (\text{stock_promo}) + \text{main0} * \text{agg_price_ndx}$$



Source: IQVIA NPA, ARCOS, and CDC. But-For Version 2: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs, plus Included Defendant/Year specifics.

Note: Depreciation Rate = x

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Table D.2

MME_EUTRX Two Break Model with Aggregate Price Index
Three-Eras

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
mme_eutrx							

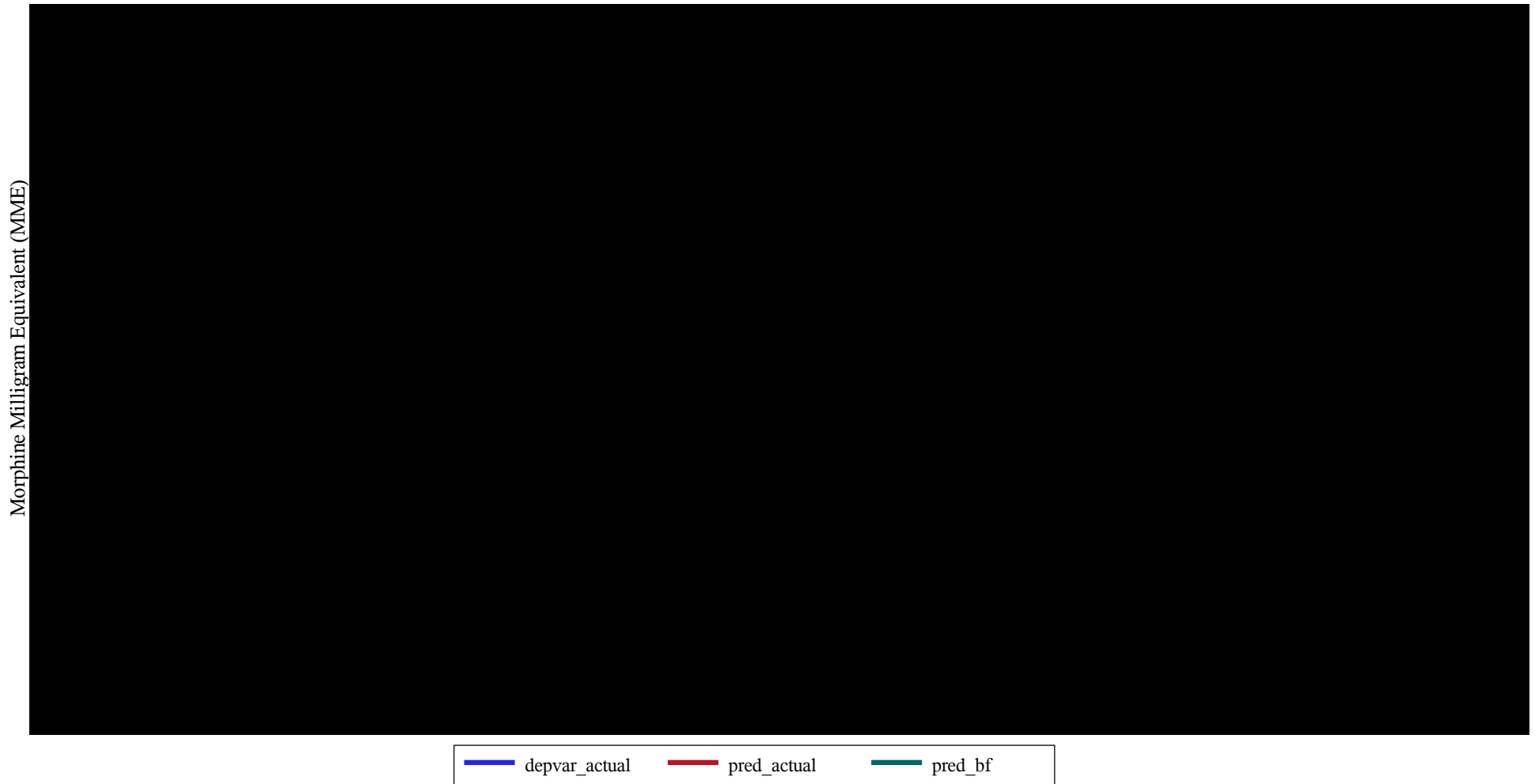
Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b1					
b2					
b3					
x					
main0					

Test Results				
Test	Type	Statistic	Pr > ChiSq	Label
Null: Slope Change=0	Wald	3139.9	<.0001	b3=0

Source: IQVIA (NPA, IPA), ARCOS, CDC.

Figure D.2

$$\text{MME_EUTRx} = (a) + (b1*ddr_Mar2002 + b2*dd_Mar2002 + b3*dt_Aug2010)*(stock_promo) + main0*agg_price_ndx$$



Source: IQVIA NPA, ARCOS, and CDC. But-For Version 2: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs, plus Included Defendant/Year specifics.
Note: Depreciation Rate = x

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Table D.3

MME_EUTRX Model Two Breaks
Three-Era Model with Price Index and Five Events

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
mme_eutrx							

Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b1					
b2					
b3					
x					
main0					
evt1					
evt2					
evt3					
evt4					
evt5					

Source: IQVIA (NPA, IPA), ARCOS, CDC.

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Table D.3

MME_EUTRX Model Two Breaks
Three-Era Model with Price Index and Five Events

The MODEL Procedure

Test Results				
Test	Type	Statistic	Pr > ChiSq	Label
Test0	Wald	13.70	0.0176	evt1, evt2, evt3, evt4, evt5
Null: Slope Change=0	Wald	301.89	<.0001	b3=0

Source: IQVIA (NPA, IPA), ARCOS, CDC.

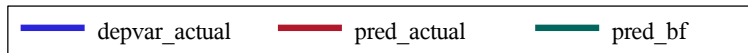
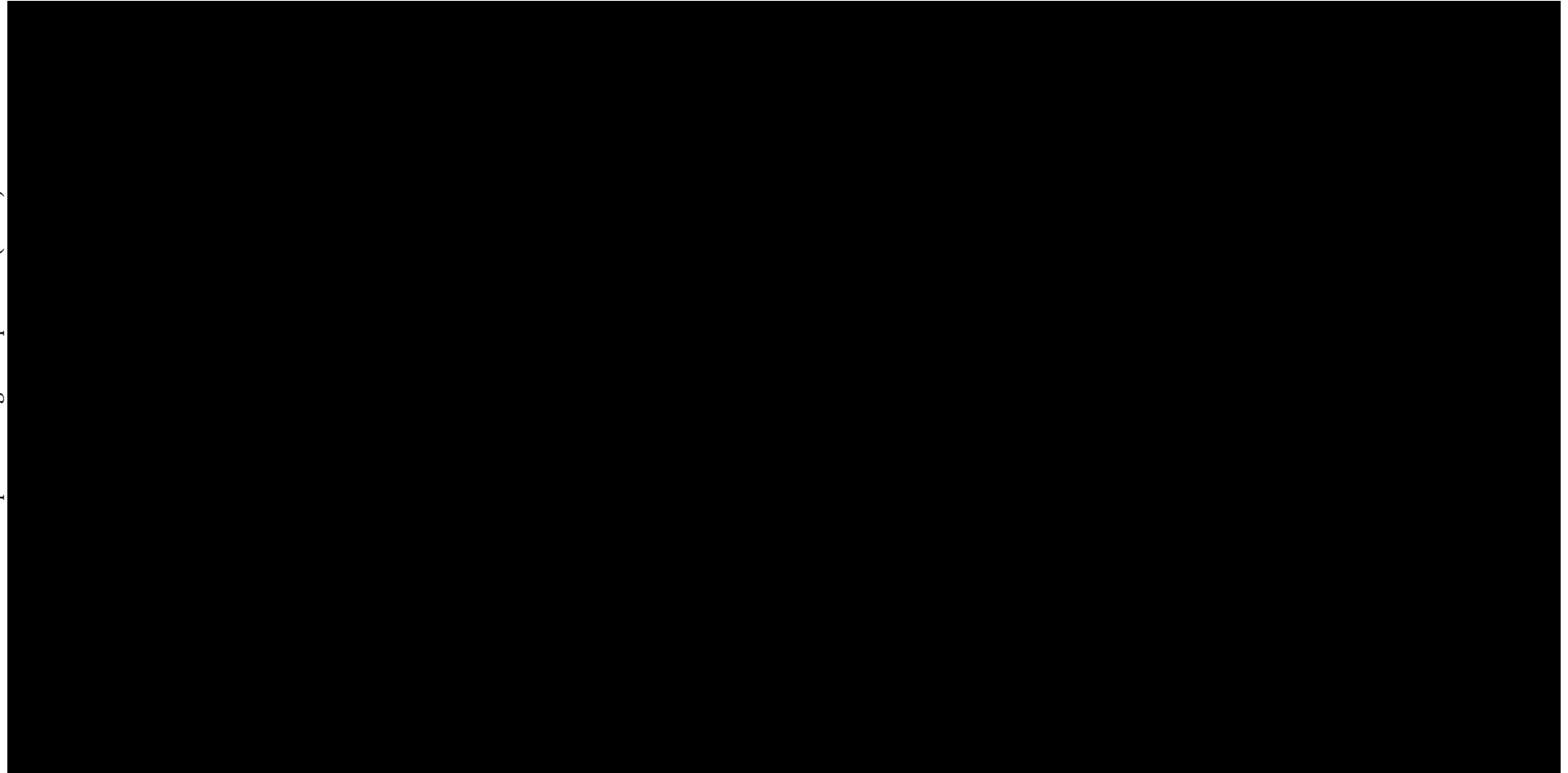
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Figure D.3

Actual, Predicted Actual, and Predicted But-For MME EUTRx

$$\text{MME_EUTRx} = (a) + (b1*ddr_Mar2002 + b2*dd_Mar2002 + b3*dt_Aug2010)*(stock_promo) \\ + main0*agg_price_ndx + evt1*dd_jan1998_APPM_APS + evt2*dd_jan1999_FSMBG + evt3*dd_jan2001_JCAHO + evt4*dd_aug2010_OxyContin + evt5*dd_oct2014_hydro_resched$$

Morphine Milligram Equivalent (MME)



Source: IQVIA NPA, ARCOS, and CDC. But-For Version 2: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs, plus Included Defendant/Year specifics.
 Note: Depreciation Rate = x

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Table D.4

Impact by Year 1995-2018
By Model

Year	(A Trx Baseline Nd)	(B Trx Twobreak Nd)	(C Trx Twobreak Nd)
Year	Pred	Pred	Pred
1995			
1996			
1997			
1998			
1999			
2000			
2001			
2002			
2003			
2004			
2005			
2006			
2007			
2008			
2009			
2010			
2011			
2012			
2013			
2014			
2015			
2016			
2017			
2018			

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Table D.4

Impact by Year 1995-2018
By Model

Year	(A Trx Baseline Nd)	(B Trx Twobreak Nd)	(C Trx Twobreak Nd)
Year	Pred	Pred	Pred

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Table D.5

Impact by Year 2006-2018
By Model

Year	(A Trx Baseline Nd)	(B Trx Twobreak Nd)	(C Trx Twobreak Nd)
Year	Pred	Pred	Pred
2006			
2007			
2008			
2009			
2010			
2011			
2012			
2013			
2014			
2015			
2016			
2017			
2018			

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Figure D.4

Impact as a Percent of Predicted Actual mme_eutrx by Model
1993-2018



Table D.6

MME_EUTRX Two Break Model with Time Trend
Three-Eras

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
mme_eutrx							

Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b1					
b2					
b3					
x					
evt0					

Test Results				
Test	Type	Statistic	Pr > ChiSq	Label
Null: Slope Change=0	Wald	139.21	<.0001	b3=0

Source: IQVIA (NPA, IPA), ARCOS, CDC.

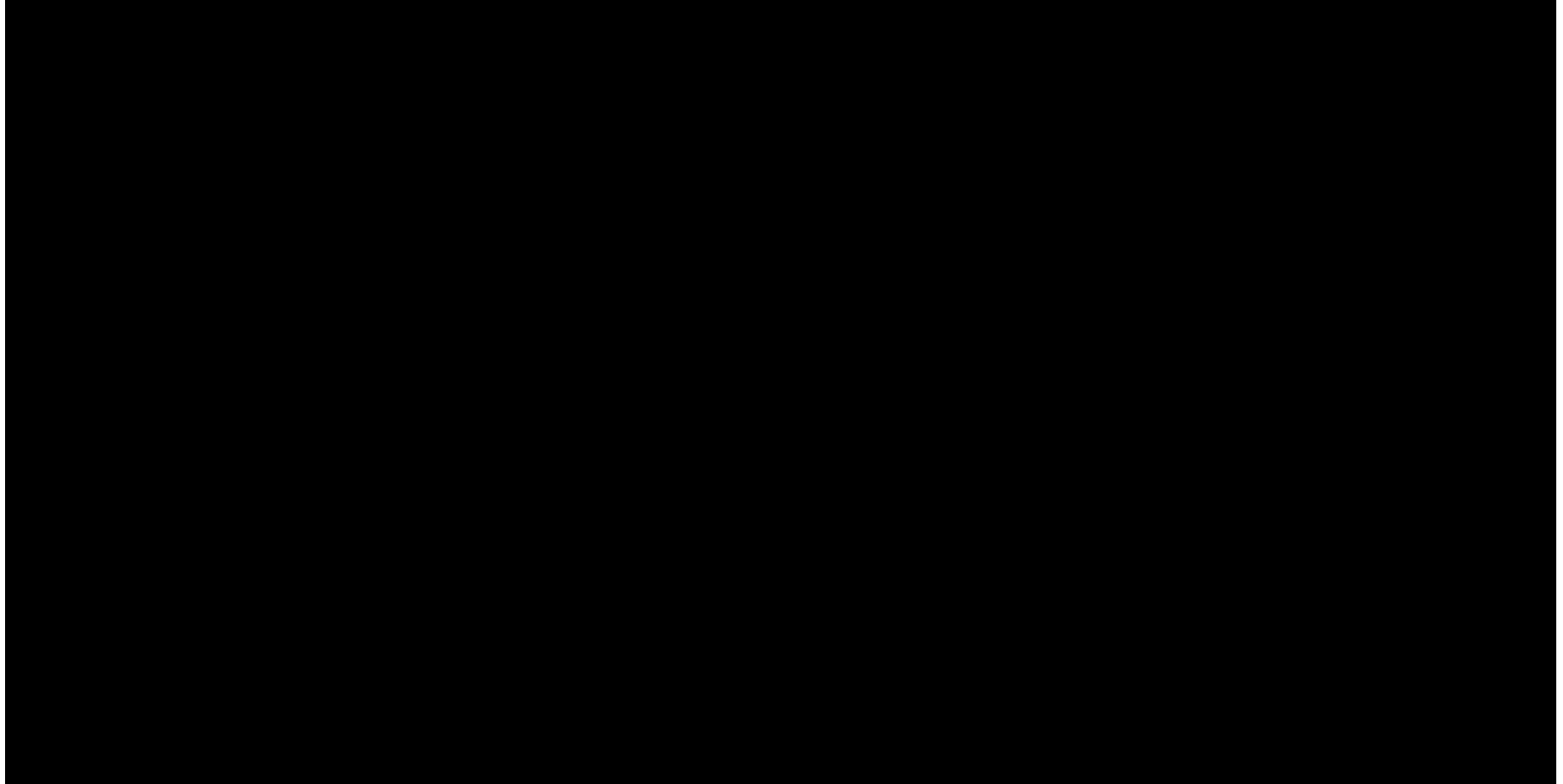
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Figure D.5

Actual, Predicted Actual, and Predicted But-For MME EUTRx

$$\text{mme_eutrx} = (a) + (b1 * \text{ddr_MAR2002} + b2 * \text{dd_MAR2002} + b3 * \text{dt_AUG2010}) * (\text{stock_promo}) + \text{evt0} * \text{dt_trend}$$

Morphine Milligram Equivalents (MME)



depvar_actual pred_actual pred_bf

Source: IQVIA NPA, ARCOS, and CDC. But-For Version 1: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs.

Note: Depreciation Rate = x

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Table D.7

EUTRX: Baseline Model: Single, Constant Estimate of Promotional Effectiveness with Price Index
No Events or Turning Points

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
eutrx							

Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b					
x					
main0					

Source: IQVIA (NPA, IPA), ARCOS, CDC.

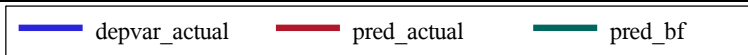
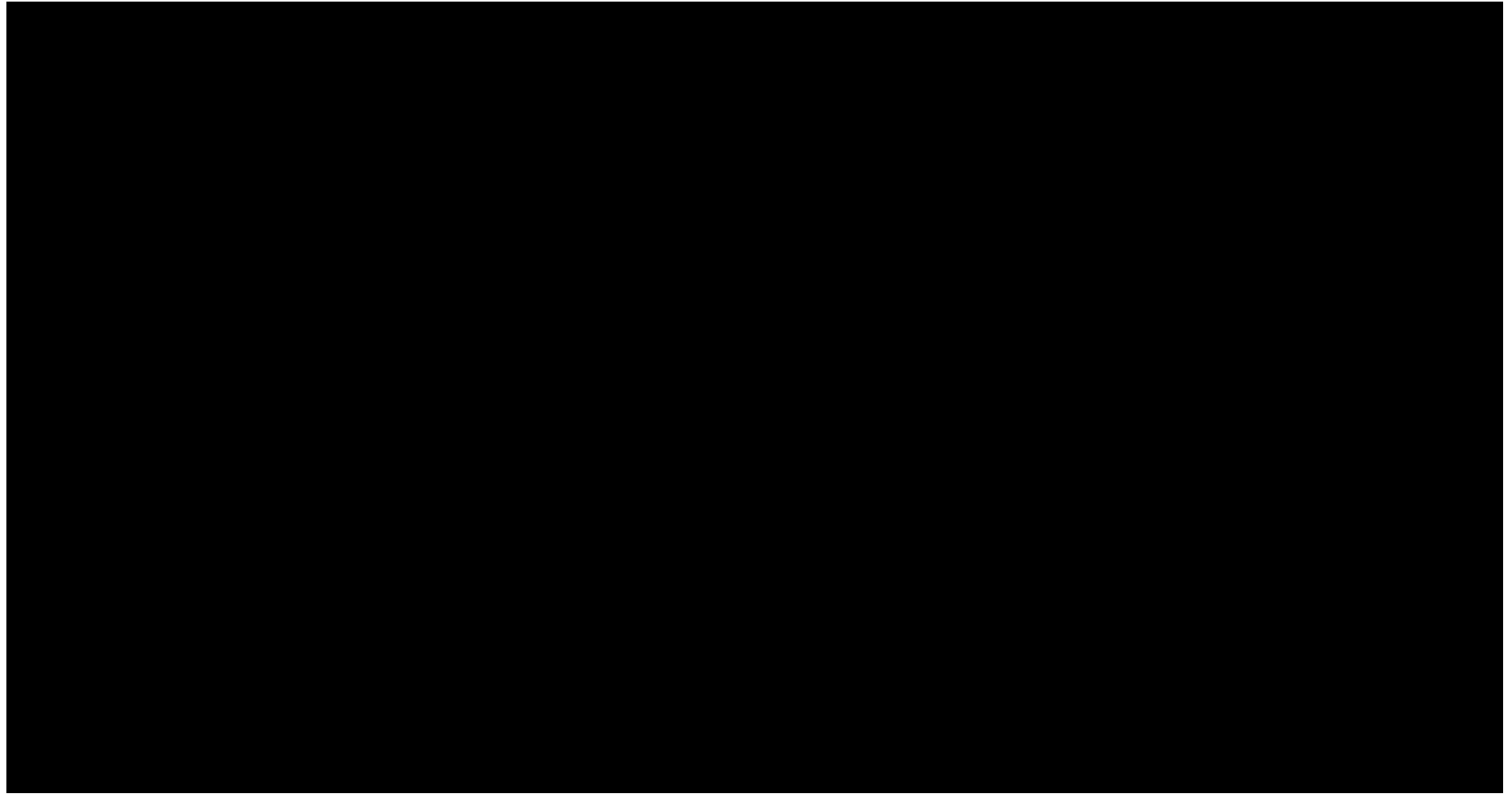
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Figure D.6

Actual, Predicted Actual, and Predicted But-For EUTRx with Baseline Model

$$\text{EUTRX} = (a) + (b) * (\text{stock_promo}) + \text{main0} * \text{agg_price_ndx}$$

Extended Units (EUTRx)



Source: IQVIA NPA, ARCOS, and CDC. But-For Version 2: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs, plus Included Defendant/Year specifics.
Note: Depreciation Rate = x

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Table D.8

EUTRX Two Break Model with Aggregate Price Index
Three-Eras

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
eutrx							

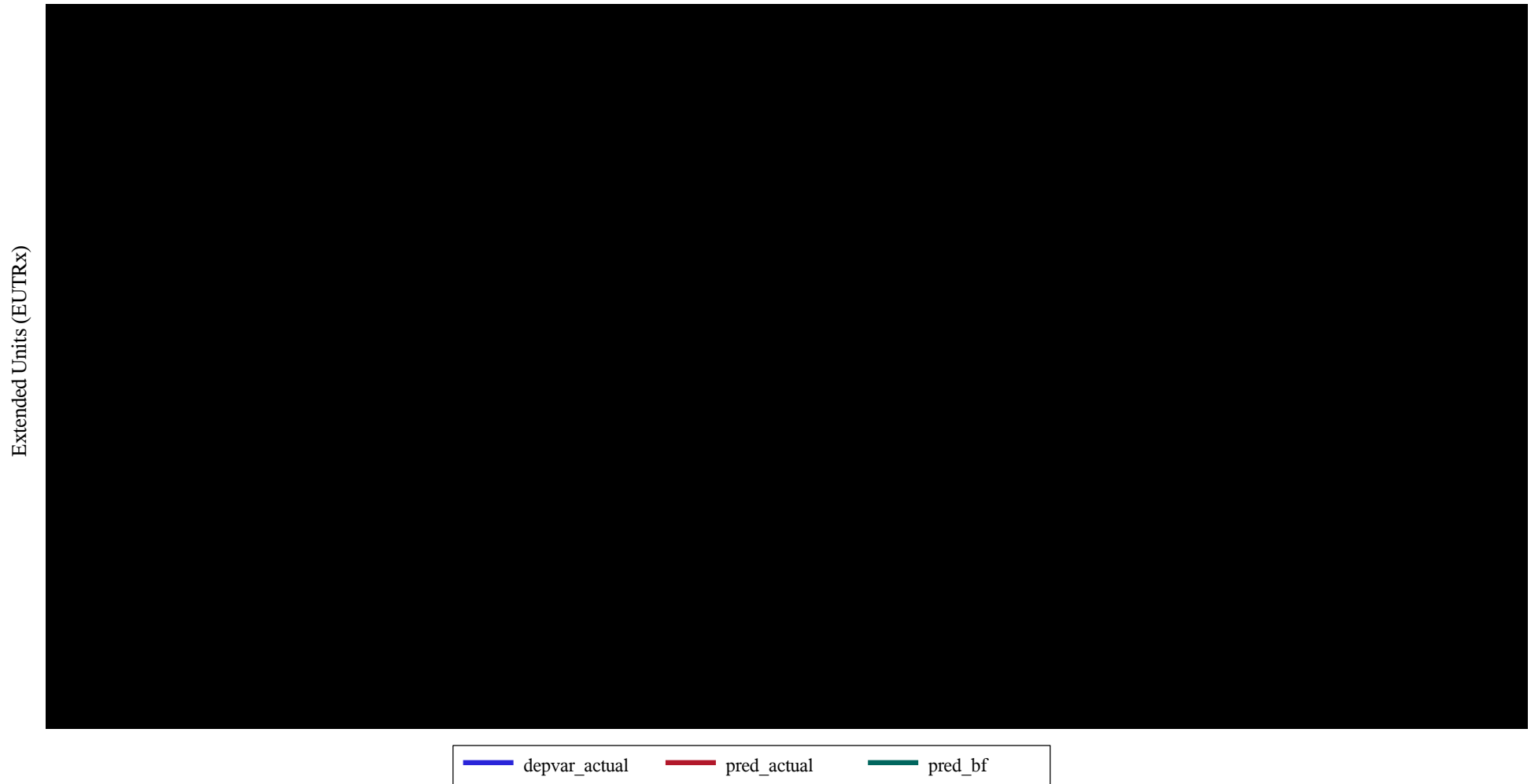
Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b1					
b2					
b3					
x					
main0					

Test Results				
Test	Type	Statistic	Pr > ChiSq	Label
Null: Slope Change=0	Wald	2910.5	<.0001	b3=0

Source: IQVIA (NPA, IPA), ARCOS, CDC.

Figure D.7

$$\begin{aligned} &\text{Actual, Predicted Actual, and Predicted But-For EUTRx} \\ \text{EUTRx} = &(a) + (b1*ddr_Mar2002 + b2*dd_Mar2002 + b3*dt_Aug2010)*(stock_promo) \\ &+ main0*agg_price_ndx \end{aligned}$$



Source: IQVIA NPA, ARCOS, and CDC. But-For Version 2: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs, plus Included Defendant/Year specifics.
Note: Depreciation Rate = x

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Table D.9

EUTRX Model Two Breaks
Three-Era Model with Price Index and Five Events

The MODEL Procedure

Nonlinear OLS Summary of Residual Errors							
Equation	DF Model	DF Error	SSE	MSE	Root MSE	R-Square	Adj R-Sq
eutrx							

Nonlinear OLS Parameter Estimates					
Parameter	Estimate	Approx Std Err	t Value	Approx Pr > t	Label
a					
b1					
b2					
b3					
x					
main0					
evt1					
evt2					
evt3					
evt4					
evt5					

Source: IQVIA (NPA, IPA), ARCOS, CDC.

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Table D.9

EUTRX Model Two Breaks
Three-Era Model with Price Index and Five Events

The MODEL Procedure

Test Results				
Test	Type	Statistic	Pr > ChiSq	Label
Test0	Wald	19.51	0.0015	evt1, evt2, evt3, evt4, evt5
Null: Slope Change=0	Wald	316.57	<.0001	b3=0

Source: IQVIA (NPA, IPA), ARCOS, CDC.

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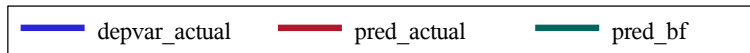
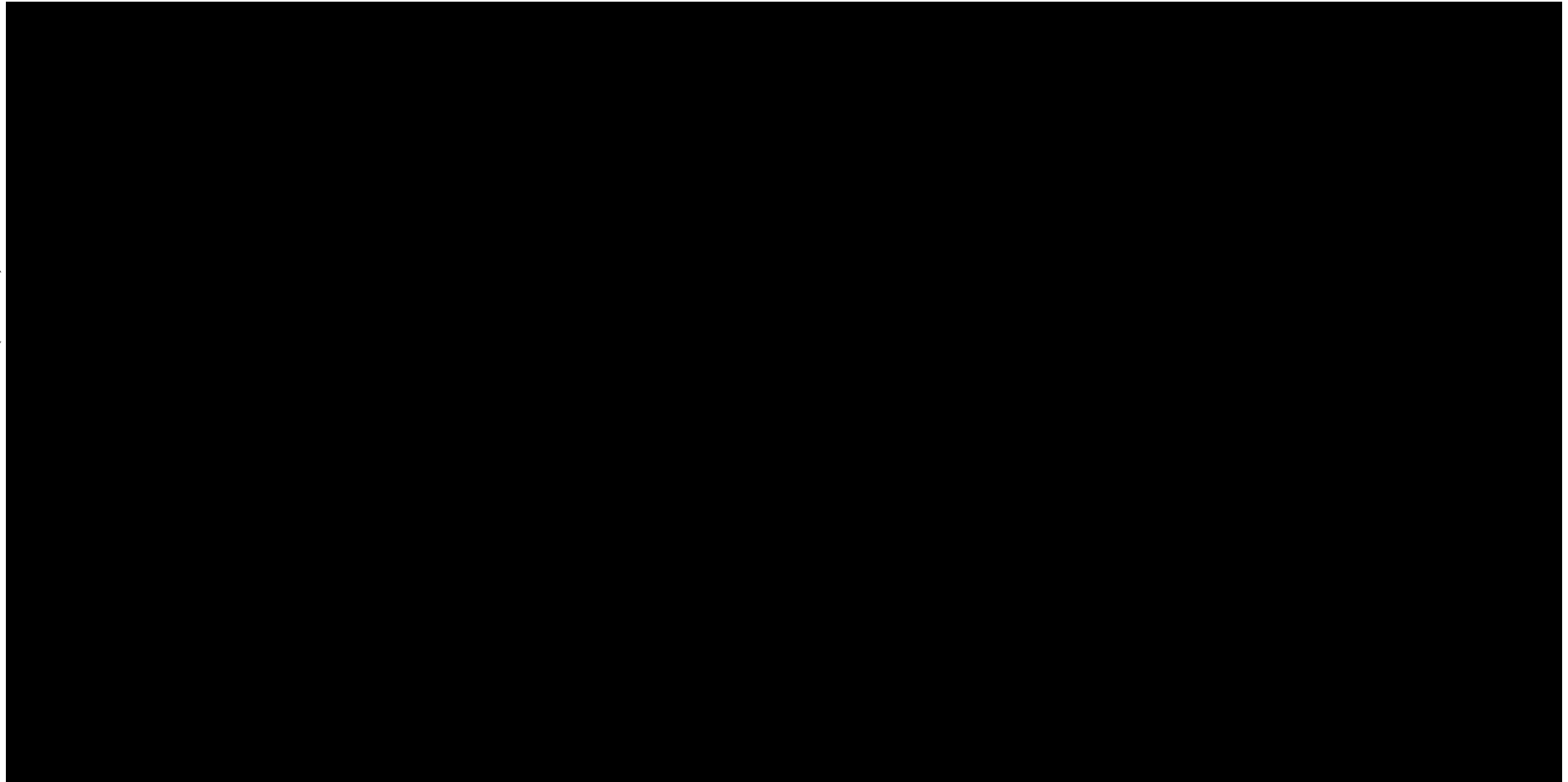
Figure D.8

Actual, Predicted Actual, and Predicted But-For EUTRx

$$\text{EUTRx} = (a) + (b1 * \text{ddr_Mar2002} + b2 * \text{dd_Mar2002} + b3 * \text{dt_Aug2010}) * (\text{stock_promo})$$

$$+ \text{main0} * \text{agg_price_ndx} + \text{evt1} * \text{dd_jan1998_APPM_APS} + \text{evt2} * \text{dd_jan1999_FSMBG} + \text{evt3} * \text{dd_jan2001_JCAHO} + \text{evt4} * \text{dd_aug2010_OxyContin} + \text{evt5} * \text{dd_oct2014_hydro_resched}$$

Extended Units (EUTRx)



Source: IQVIA NPA, ARCOS, and CDC. But-For Version 2: Starting 1995 But-For promotion is by Non-Defendants for Non-Defendant drugs, plus Included Defendant/Year specifics.
 Note: Depreciation Rate = x

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